RISTANALYSIS IN OCCUPATIONAL AND ENVIRONMENTAL HEALTH

September 4 -- 6, 1991

OFFICE OF CONTINUING EDUCATION
HARVARD SCHOOL OF PUBLIC HEALTH
BOSTON, MASSACHUSETTS

025545673

Administrative Materials

PROGRAM AGENDA
FACULTY ROSTER
PARTICIPANT ROSTER
PROGRAM EVALUATION INSTRUMENT
MAPS AND NOTES (BLUE SHEETS)

RISK ANALYSIS IN OCCUPATIONAL & ENVIRONMENTAL HEALTH

September 4 - 6, 1991

Course Co-Leaders: Richard Wilson & Dade W. Moeller

| | <u>AGENDA</u> |
|--|---------------|
|--|---------------|

| DAY/TIME | TOPIC | SPEAKER | | | |
|----------------------------|--|------------|--|--|--|
| Wednesday, Sept | tember 4 | | | | |
| • | Course Introduction | | | | |
| 8:30 - 9:00 | Welcome | Moeller | | | |
| 9:00 - 10:00 | Introduction to Risk Analysis | Wilson | | | |
| 10:00 - 10:15 | Refreshment Break | | | | |
| 10:15 - 11:30 | FDA Approach to Risk Assessments | Scheuplein | | | |
| | Introduction to Discussion Session | | | | |
| 11:30 - 12:15 | Introduction to Background Materials on: 1. ALAR (daminozide) 2. Dioxin 3. Lead | Moeller | | | |
| 12:15 - 1:00 | Lunch | | | | |
| | Tools in Risk Analysis | | | | |
| 1:00 - 2:15 2:15 - 2:30 | Applications of Epidemiology (Benzen - Case Study) Refreshment Break | Cole | | | |
| 2:30 - 3:45 | Use of Animal Data as Predictors of Human Risk | Crouch | | | |
| 3:45 - 5:00 | Endpoints Other Than Cancer | Brain | | | |
| Thursday, September 5 | | | | | |
| | Cancer & Cancer Modeling | | | | |
| 8:30 - 9:30 | What is Cancer? | Upton | | | |
| 9:30 - 9:45 | Refreshment Break | | | | |

| 9:45 - 11:15 | Cancer Modeling | Cohen |
|-----------------|--|---------------------|
| 11:15 - 11:30 | Break | |
| | Applications of Expert Judgment | |
| 11:30 - 12:15 | Applications of Expert Judgment in Risk Analysis | Moeller |
| 12:15- 1:15 | Lunch | |
| | Exposure Assessment | |
| 1:15 - 2:45 | The Respiratory System as an Entry for Exposure | Valberg |
| 2:45 - 3:15 | Refreshment Break | |
| 3:15 - 4:45 | Assessment of Exposures | Ryan |
| Friday, Septemb | er 6 | |
| | Regulatory Aspects | |
| 8:30 - 9:30 | Legislative & Regulatory Aspects of Risk | Brown |
| 9:30 - 9:45 | Refreshment Break | |
| Risk_A | <u>Discussion Session -</u> nalysis for Specific Contaminants | |
| 9:45 - 11:15 | 1. ALAR (Daminozide) | Graham |
| 11:15 - 12:30 | 2. Dioxin | Birnbaum |
| 12:30 - 1:15 | Lunch | |
| 1:15 - 2:00 | 3. Lead | Hu |
| 2:00 - 2:30 | General Discussion | Staff |
| 2:30 - 2:45 | Refreshment Break | |
| | Course Closing | |
| 2:45 - 3:30 | Risk in Perspective | Wilson |
| 3:30 - 3:45 | Course Critique & Evaluation | Moeller & Wilson |

RISK ANALYSIS IN OCCUPATIONAL AND ENVIRONMENTAL HEALTH

September 4--6, 1991

FACULTY ROSTER

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RISK ANALYSIS IN OCCUPATIONAL AND ENVIRONMENTAL HEALTH

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Carry your purse close to your body.

Don't leave valuables in your room, use a hotel safe deposit box.

Abide by common sense: if something looks suspicious, avoid it and report it.

and Kern FROM: David A. S. Klipp, Program Coordinator

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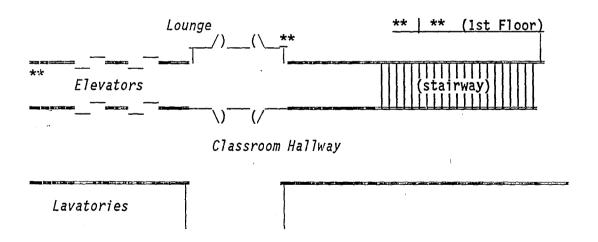
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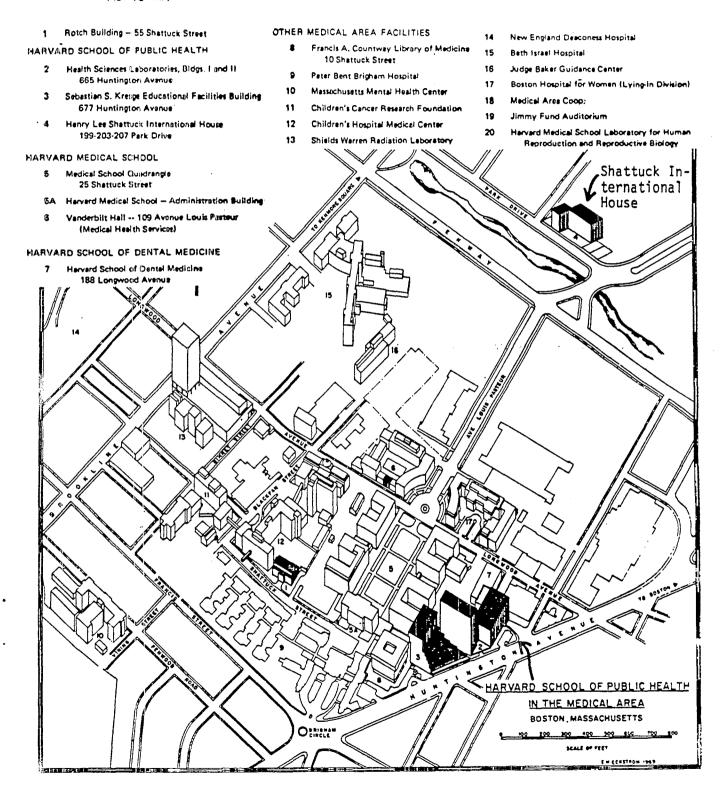


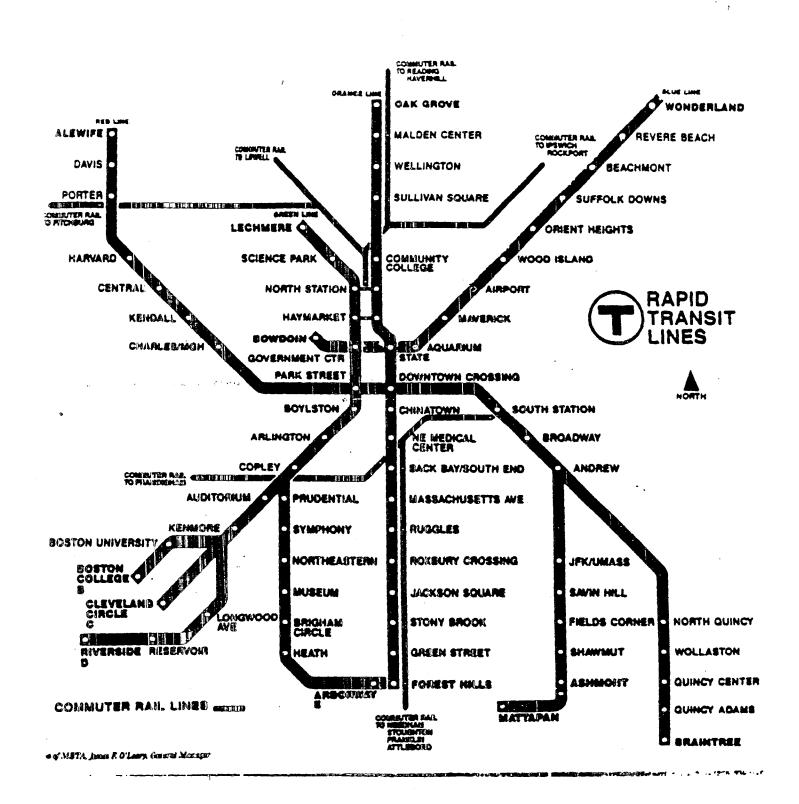
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Acknowledging the limited number of public telephones available here, we ask that you please try to consider keeping your calls brief and to a minimum.

HARVARD MEDICAL AREA

(KEY TO MAP)





2025545686

Moeller

Wednesday, September 4

Course Introduction

| 8:30 - 9:00 | Welcome | Moeller |
|---------------|--|------------|
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Risk Assessment for Carcinogens: A Comparison of Approaches of the ACGIH and the EPA

Michael C.R. Alavanja, Charles Brown, Robert Spirtas, Co and Manuel Gomez

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The relative carcinogenic potency of 16 chemicals evaluated by both the U.S. Environmental Protection Agency (EPA) and the Chemical Substances Threshold Limit Values (CS-TLV) Committee of the American Conference of Governmental Industrial Hygienists (ACGIH) were compared. The estimated cancer risk resulting from occupational exposure to the threshold limit values (TLVs) were also computed using dose-response curves developed as a part of EPA quantitative risk assessments.

Substantial agreement between the EPA and the CS-TLV Committee was found when the relative potency of these carcinogens was compared. Use of EPA's risk model to estimate lifetime cancer risk from occupational exposure at the TLV levels often resulted in high cancer risk estimates. The approaches used to assess cancer risk by both groups is described and a suggestion is made for incorporating existing quantitative risk assessments into the TLV evaluation procedure. Alavanja, M.C.R.; Brown, C.; Spirtas, R.; Giomez, M.: Risk Assessment for Carcinogens: A Comparison of Approaches of the ACGIH and the EPA. Appl. Occup. Environ. Hyg. 5:510–517; 1990.

Introduction

The Chemical Substances Threshold Limit Values (CS-TLV) Committee of the American Conference of Governmental Industrial Hygienists (ACGIH) has been reviewing its policies and procedures regarding carcinogens. Spirtas *et al.* (1985) described the current process the CS-TLV Committee uses to make the qualitative decision to designate a chemical as a workplace carcinogen and the quantitative decision to recommend levels of exposure for the guidance of industrial hygienists. (1) Threshold limit values (TLVs) (for carcinogens as well as other toxic agents) are time-weighted averages (TWAs) for a normal 8-hour workday, 40-hour workweek. The TLV is set for inhalation ex-

posure, with special notifications for agents where absorption from skin exposure is important. The TLV is assumed to be protective for "nearly all workers" assuming the workers to be healthy adults.⁽¹⁾ TLVs are guidelines for good work practices to be used only by professional industrial hygienists. For substances which cause chronic diseases such as cancer, however, there may not be a sharp cutoff point (threshold) between effect and no effect; it is, therefore, important that professional judgment be used in monitoring and protecting workers exposed to such substances.

When deciding on guidelines for carcinogens, the CS-TLV Committee gives greatest weight to epidemiologic studies having data on quantitative exposure levels.(1) Such substances receive an A1 categorization and are called "Confirmed Human Carcinogens." Next in importance, and more typically available, are mammalian toxicologic studies having whole-body bioassays. Such substances are given an A2 designation and are called "Suspected Human Carcinogens." In reviewing the key experimental toxicology studies, the Committee considers route of entry (greatest weight given to inhalation studies), dose-response gradient, potency, mechanism of action, cancer site, time-totumor, length of exposure, and underlying incidence rate for the type of cancer and species under study. Replication of results is important, especially if comparable in different species. Other types of studies are useful in confirming

This article represents the views of the authors and not those of the American Conference of Governmental Industrial Hygienists or its Chemical Substances Threshold Limit Values Committee, or those of the U.S. Department of Health and Human Services, the National Institutes of Health, and the National Cancer Institute.

that a substance is a carcinogen but are not usually helpful in setting a TLV. A safety factor is often applied to establish a TLV for carcinogens, by taking the lowest level known to induce cancer (or the no-effect level) and then dividing that by an arbitrary factor, such as 10 or 100. The CS-TLV Committee, realizing the imprecision of setting TLVs for carcinogens, recommends that, for all carcinogens having a TLV, "worker exposure by all routes should be carefully controlled to levels as low as reasonably achievable (ALARA) below the TLV."

In the early 1970s, the U.S. Environmental Frotection Agency (EPA) developed an approach that was different from that of the CS-TLV Committee. Early decisions by the EPA conveyed the idea that the only acceptable degree of regulation of carcinogens would be a total ban on exposures.(3,4) However, the impracticality of achieving zero risk on a broad scale for a large number of economically important chemicals became increasingly apparent to many, including the U.S. Congress. As a result, the EPA in 1976 became the first federal agency to adopt formal guidelines embracing a two-step process of risk assessment. The first step is a determination of whether a particular substance constitutes a cancer risk, i.e., hazard identification. The second step includes a quantitative risk assessment (QRA) as a key component of determining the degree of regulatory action needed to protect the public. (5)

As part of the QRA process, the EPA computes dose-response curves, makes low-dose extrapolations, and estimates the size and degree of exposure of the exposed populations in order to estimate the number of excess cancers expected in the total U.S. population. The rationale and procedures for the EPA approach are used to guide regulatory actions which are meant to protect each member of the general public over a lifetime against exposure via inhalation or ingestion. (6) Regulatory action is taken only after the results of the QRA are integrated with engineering data and with social, economic, and political concerns. (7)

Confusion has arisen from the different approaches used by the CS-TLV Committee and the EPA in estimating risk. Although the TLVs continue to be used widely by professional industrial hygienists around the world to evaluate the safety of workplace exposures, the QRA approach is viewed by some as more objective. Recently, criticism of TLVs has focused attention on the objectivity and scientific standards of the CS-TLV Committee. (8) Several examples were given of chemical substances for which unpublished data (primarily from the files of industrial companies) were important in setting the recommended TLV. Since, in many instances, the TLV is the only number available to industrial hygienists, it is important that the CS-TLV Committee's policies and procedures regarding carcinogens be reviewed to assess the results of the current TLV approach. We believe a quantitative comparison of the EPA and the TLV approaches may provide some important information regarding this assessment.

Reflecting on some of these issues, Andersen⁽⁹⁾ presented a critical review of quantitative risk assessment in

occupational health in the 1988 Herbert E. Stokinger Lecture, concluding that, "Quantitative Risk Assessment is not just coming to the occupational environment. It is here now and is an issue to be reckoned with by everyone of us in the industrial hygiene profession."(9) In his review, Andersen suggests that QRA during the past 13 years has been "damned" by its misapplication. Overly conservative quantitative approaches to predicting risk would lead to risk estimates that "greatly restrict commercial operations, decrease our ability to compete in world markets, and lead to large expenditures to change work practices with no concomitant increase in health protection." He went on to suggest that the problems faced by the use of overly conservative techniques can be overcome in part by the use of recent cancer models that have greater biological relevance, e.g., the physiologically based pharmacokinetics models (PB-PK)(10) and the Moolgavkar, Venzon, Knudson (MVK) models.(11) Although the theoretical appeal of these cancer models is clear, the bulk of the QRAs developed and published since 1976 have come from regulatory agencies which have not used these new techniques. We cannot compare current TLVs to the results of risk assessments using the MVK or PB-PK approaches; however, comparing established TLVs for carcinogens with the results of the EPA QRAs may help determine whether, and under what circumstances, the CS-TLV Committee may consider using ORAs as part of its decision-making process. This article presents a comparison between the ACGIH TLVs and the EPA QRAs for the 16 chemical carcinogens that have been evaluated by both groups. These ORAs were chosen for comparison since they are the largest available collection of risk assessments developed by a standard methodologic approach.

Methods and Results

The comparison reported here is derived from the ACGIH 1988-1989 list of TLVs(12) and an EPA list of carcinogens taken from the Integrated Risk Information System. (13) The ACGIH list contains over 700 agents of which 55 are classified by the Committee as carcinogens in the adopted list plus 3 in the Notice of Intended Changes List. These 55 substances are listed along with their TLVs, where available, in Table I. The EPA list, in Table II, contains 54 agents, including a substantial number of pesticides and nitrosamines for which a unit risk factor for inhalation exposure is available. The EPA's unit risk factor is a conservatively estimated risk to humans from constant lifetime exposure of breathing contaminated air at a level of 1 μg/m³. This risk estimate is derived from the available results of animal bioassays, biochemical studies, and epidemiologic studies. To assure safety, conservative assumptions are used to supplement missing or unknown information (e.g., using results from the most sensitive animal species and the linearized multistage dose-response model and extrapolating using the upper 95 percent confidence limit of the experimental evidence).

The ACGIH TLVs are compared with the EPA QRAs

TABLE I. Chemical Substances Classified as Carcinogens by ACGIH with Their Respective TLVs (1988-1989 Adopted Values)

| Substance | TLV | Substance | TLV | |
|--|-------------------------|---|-----------------------------------|--|
| Acrylamide—Skin ^A | 0.03 ma/m³ | Ethylene dibromide—Skin | | |
| Acrylonitrile—Skin ⁴ | 4.5 ma/m ³ | Ethylene oxide ⁴ | 1.8 mg/m ³ | |
| 4-Aminodiphynyl—Skin | 8 | Formaldehyde ^A | 1.5 mg/m ³ | |
| Antimony trioxide production | _ | Hexachlorobutadiene—Skin* | 0.21 mg/m³ | |
| Arsenic trioxide production | | Hexamethyl phosphoramide—Skin | | |
| Asbestos | | Hydrazine—Skin | 0.13 ma/m³ | |
| Amosite | 0.5 fiber/cc | 4,4'-Methylene bis(2-chloroaniline)-Skin | 0.22 mg/m ³ | |
| Chrysotile | 2 fibers/cc | Methylene chioride (Dichloromethane) ^A | 175 mg/m ³ | |
| Crocidolite | 0.2 fiber/cc | 4,4'-Methylene dianiline | 0.81 ma/m³ | |
| Other forms | 2 fibers/cc | Methyl hydrazine—Skin | 0.35 ma/m ³ | |
| Benzene ^A | 32 ma/m ³ | Methyl iodide—Skin | 12 mg/m³ | |
| Benzidine—Skin | в | β-Naphthylamine | 8 | |
| Benzo(a)pyrene | | Nickel sulfide roasting, furne & dust | 1 mg/m³, as Ni B | |
| Beryllium ^A | 0.002 ma/m³ | 4-Nitrodiphenyl | | |
| 1,3-Butadien; ^A | 22 mg/m³ | 2-Nitroprogane | 35 mg/m ³ | |
| Carbon tetrachloride—Skin ⁴ | 31 mg/m ³ | N-Nitrosodimetrytamine—Skin | _ | |
| Chloroform* | 49 ma/m ³ | N-Phenyl-beta-naphthylamine | | |
| pis-(Chloromethyl)ether* | 0.005 mg/m ³ | Phenylhydrazine—Skin | 22 mg/m³ | |
| Chlormethyl rneityl ether | _ | Propane sultone | • | |
| Chromates of lead, as Cr | 0.05 mg/m ³ | B-Propiolactone | 1.5 mg/m³ | |
| Ohromite ore processing (chromate) | 0.05 mg/m³, as Cr | Propylene imine—Skin | 4.7 mg/m ³ | |
| Chromium (Vi), certain water insoluble compounds ^A | 0.05 mg/m³, as Cr | o-Tolidine—Skin | | |
| Chrysene | | o-Toluidine—Skin | 9 mg/m³ | |
| Coal tar pitch volatiles | 0.2 mg/m³, as benzene | p-Toluidine—Skin | 9 mg/m³ | |
| The state of the s | solubles | Vinyl bromide | 22 mg/m³ | |
| 3.3'-DichlorobenzidineSkin | | Vinyl chloride | 13 mg/m ³ | |
| Dimethyl carbumoyl chloride | | Vinyl cyclohexene dioxide—Skin | 57 mg/m³ | |
| I,1-Dimethylhydrazine—Skin | 1.2 mg/m ³ | Zinc chromates | 0.01 mg/m³, as Cr | |
| Dimethyl sulfale—Skin | 0.5 mg/m ³ | LITE GROWING | | |
| | Notice of Intended Cha | inges (for 1988–1989) | | |
| Cadmium and compounds ^A 0.1 mg/m ³ | Ethyl acrylate | 20 mg/m ³ Xytidine (mixed is | omers)—Skin 2.5 mg/m ² | |

AChemicals contained on both the TLV and EPA carcinogen list.

in two ways: 1) do the ACGIH and EPA place these chemicals in the same order of toxicity? and 2) what level of risk do the EPA unit risk factors imply from exposure to the ACGIH's TLVs? The EPA dose—response assessment commonly begins with the multistage model,

$$P(d) = 1 - \exp(q_1 d + q_2 d^2 + ... + q_k d^k),$$

puts an upper 95 percent confidence limit on the linear term of the dose–response (q_1^*) based on a statistical evaluation of animal bioassay data (with consideration of species, route of administration, duration of exposure and followup, and other experimental design criteria deemed most relevant to human risk assessment), and then uses the linearized multistage model (only the linear term is included) to estimate the risk of lifetime exposure to low doses. Because the linearized multistage model used by the EPA for its unit risk factor is equivalent to the single hit model, our estimate of lifetime risk of developing cancer from occupational exposure is based on the model,

Prob (d) =
$$1 - \exp(-\alpha d)$$
,

where Prob(d) is the lifetime probability of developing cancer from exposure to a daily level of d $\mu g/m^3$ during a working lifetime of a 40-hour workweek/168-hour week, a 50-week/workyear, a 40-year career, and an average life

span of 74 years. The slope of this dose–response curve (α) directly indicates cancer risk, thus a larger slope implies a larger risk at the same dose. The slope is derived from the EPA unit risk factor and is adjusted as follows to reflect different exposure situations.

To adjust for different exposure durations, we use the simple assumption that the dose-response slope for occupational exposure is $(40/168) \times (50/52) \times (40/74) = 0.124$ of the complete lifetime exposure slope. The EPA assumes a normal respiration rate of 20 cubic meters in a 24-hour period while we assume a rate of 10 cubic meters in an 8-hour working day. Therefore, to adjust for different breathing rates for working and nonworking persons, we assume the occupational exposure slope is (10/8)/(20/24) = 1.5 times the EPA slope.

Figure 1 displays the comparison of the ACGIH and EPA arrangements of the 16 common agents in decreasing order of risk (increasing TLV level and decreasing unit risk order). The spearman rank correlation coefficient for these two orderings is r=0.78 implying substantial, yet imperfect, agreement. The major disagreements are the orderings of hexachlorobutadiene, 1,3-butadiene, vinyl chloride, formaldehyde, and chloroform. The ACGIH has hexachlorobutadiene with a greater carcinogenic risk than 1,3-butadiene, and vinyl chloride with a greater risk than

⁸ Substance designed by CS-TLV Committee as a confirmed human carcinogen without a TLV. Workers exposed to this substance should be "properly equipped to wirtually eliminate all exposure." 22

chloroform, while the EPA reverses this order. In addition, formaldehyde is substantially higher on the ordering by ACGIH than by EPA. In establishing TLVs for vinyl chloride and chloroform, the CS-TLV Committee probably weighted heavily the positive epidemiologic evidence for vinyl chloride, in deciding to establish a relatively more protective value for vinyl chloride than for chloroform. The TLV for formaldehyde is based primarily on prevention of eye, nose, and throat irritation. These acute effects have been observed in humans at levels below the lowest effect seen for carcinogenicity in rodents. The discrepancy for 1,3-butadiene can be explained, in part, by the CS-TLV Committee minimizing the relevance of an animal bioassay which induced angiosarcomas of the heart, a rare tumor in humans.

Table III gives the TLVs and adjusted unit risk for these agents along with the EPA's estimate of daily occupational exposure levels corresponding to lifetime cancer risks of one in a million and one in a thousand. This table also gives an estimate of the lifetime risk from occupational exposure to a daily level at the TLV. Eight of these 16 estimated lifetime cancer risks from occupational exposure to the TLV lie between 1 and 10 percent with the two highest estimates being chloroform at 19 percent and 1,3-butadiene at 68 percent while the two lowest estimates are hexachlorobutadiene at 0.1 percent and beryllium at 0.09 percent. On the average, the TLVs for these 16 agents are over 25 times greater than the EPA estimated daily exposure level associated with a risk of 1/1000. Table III also

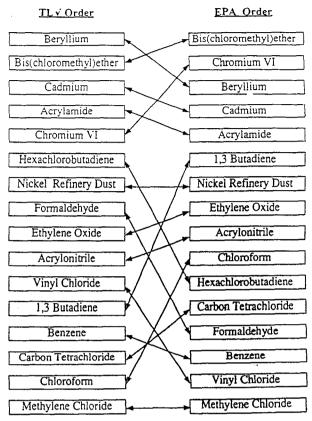


FIGURE 1. Ordering of chemicals by estimated risk by the Chemical Substances TLV Committee and the U.S. Environmental Protection Agency.

TABLE II. Chemicals Carcinogens for Which Quantitative Risks Have Been Computed for Inhalation Exposure by U.S. EPA's Carcinogen Assessment Group

| Compounds | Unit Risk Factors* | Compounds | Unit Risk Factors* |
|--|------------------------|-----------------------------|--------------------------|
| Acetaldehyde | 2.2 × 10 ⁻⁶ | 1,2-Diphenythydrazine | 4.5 × 10 ⁻¹ |
| Acrylamide | 1.3×10^{-3} | Epichlorohydrin | 1.2 × 10-6 |
| Acrylonitrile | 6.8×10^{-5} | Ethylene oxide | 1.8 × 10−² |
| Aldrin | 4.9×10^{-3} | Formaldehyde | 1.1 × 10-4 |
| Arsenic | 4.3×10^{-3} | Heptachlor | 1.3×10^{-3} |
| Asbestos | 2.3×10^{-1} | Haptachlor epoxide | 2.6×10^{-3} |
| Azobenzene | 3.1×10^{-5} | Hexachlorobutadiene | 2.2 × 10 ⁻⁵ |
| Benzene | 8.3 × 10 ⁻⁶ | Hexachlorocyclohexane | 2.1 × 10 ⁻⁵ |
| Benzidene | 6.7 × 10−² | technical grade | 2.0 × 10 ⁻¹ |
| Beryllium | 2.4×10^{-3} | alpha isomer | . 1.8 × 10 ⁻³ |
| 1,3-Butadiene | 2.8 × 10 ⁻⁴ | beta isomer | 5.3 × 10-4 |
| Cadmium | 1.8×10^{-3} | Hexachlorodibenzodioxin | 1.3 × 10 ⁻⁴ |
| Carbon tetrachloride | 1.5 × 10⁻⁵ | Hydrazine/Hydrazine sulfate | 4.9 × 10 ⁻³ |
| Chlordane | 3.7×10^{-5} | Nickel refinery dust | 2.4 × 10-4 |
| bis(2-chloroethyl)ether | 3.3 × 10-⁴ | Nickel subsulfide | 4.8 × 10 ⁻⁴ |
| Chloroform | 2.3 × 10 ⁻⁵ | Nitroso-dimethylamine | 1.4×10^{-2} |
| bis(chloromethyl)k:ther | 6.2×10^{-2} | Di-butylamine | 1.6×10^{-3} |
| Chromium VI | 1.2×10^{-2} | Diethylnitrosamine | 4.3 × 10 ⁻² |
| DDT | 9.7×10^{-5} | N-nitrosopyrrolidine | 6.1 × 10 ⁻⁴ |
| 1.2-Dibromoethane | 2.2 × 10 ⁻⁴ | 1,1,1,2-Tetrachioroethane | 7.4 × 10 ⁻⁶ |
| DibutyInitrosamine: | 1.6×10^{-3} | 1,1,2,2-Tetrachloroethane | 5.8 × 10 ⁻⁵ |
| 1.2-Dichloroethane | 2.6×10^{-6} | Toxaphene | 3.2 × 10 ⁻⁴ |
| 1,1-Dichloroethylene (Vinylidene chloride) | 5.0×10^{-5} | 1,1,2-Trichloroethane | 1.6 × 10 ⁻⁵ |
| Dichloromethane (Methylene chloride) | 4.1×10^{-5} | Trichloroethylene | 1.3×10^{-6} |
| Dieldrin | 4.6×10^{-3} | 2,4,6-Trichlorophenol | 5.7 × 10 ⁻⁶ |
| Diethylnitrosamine | 4.3×10^{-2} | Vinyl chloride | 7.1 × 10-6 |
| Dimethylnitrosamine | 1.4×10^{-2} | | |

Estimated risk to humans from constant lifetime exposure of breathing contaminated air at a level of 1 µg/m³.

TABLE III. Estimated Lifetime Cancer Risk from Occupational Exposure to the TLV

| | IARC TLV | Adjusted | Daily Exposure (µg/m³) Associated with Risk of | | Estimated Lifetime Cancer Risk from | |
|---|----------|----------|--|----------------------|--|-----------------|
| Substance | Class | μg/m³ | Unit Risk* | 1/10* | 1/103 | Exposure to TLV |
| Acrylamide | 2B | 30 | 2.4 × 10-4 | 4.2×10^{-3} | 4.2 | 0.0072 |
| Acrylonitrile | 2A | 4500 | 1.3×10^{-5} | 7.7×10^{-2} | 7.7×10^{1} | 0.057 |
| Benzene | 1 | 30000 | 1.5×10^{-6} | 6.7×10^{-1} | 6.7×10^{2} | 0.044 |
| Beryllium | 2A | 2 | 4.5×10^{-4} | 2.2×10^{-1} | 2.2 | 0.0009 |
| 1,3-Butadiene | 2B | 22000 | 5.2×10^{-5} | 1.9×10^{-2} | 1.9×10^{1} | 0.68 |
| Cadmium | 2A | 10 | 3.3×10^{-4} | 3.0×10^{-3} | 3.0 | 0.0033 |
| Carbon tetrachloride | 2B | 30000 | 2.8×10^{-6} | 3.6×10^{-1} | 3.6×10^{2} | 0.081 |
| Chloroform | 2B | 50000 | 4.3×10^{-6} | 2.3×10^{-1} | 2.3×10^{2} | 0.19 |
| bis(chloromethyl)ether | 1 | 5 | 1.2×10^{-2} | 8.3×10^{-5} | 8.3×10^{-2} | 0.058 |
| Chromium (VI) | 1 | 50 | 2.2×10^{-3} | 4.5×10^{-4} | 4.5×10^{-1} | 0.10 |
| Dichloromethane (Methylene chloride) | 2B | 175000 | 7.6×10^{-7} | 1.3 | 1.3×10^{3} | 0.12 |
| Ethylene oxide | 2A | 2000 | 2.0×10^{-5} | 5.0×10^{-2} | 5.0×10^{1} | 0.039 |
| Formaldehyde | 2A | 1500 | 2.4×10^{-6} | 4.2×10^{-1} | 4.2×10^{2} | 0.0036 |
| Hexachlorobutaciene | 3 | 240 | 4.1×10^{-6} | 2.4×10^{-1} | 2.4×10^{2} | 0.00098 |
| Nickel refinery dust | 1 | 1000 | 4.5×10^{-5} | 22×10^{-2} | 2.2×10^{1} | 0.044 |
| Vinyl chloride | 1 | 10000 | 1.3 × 10 ⁻⁶ | 7.7×10^{-1} | 7.7×10^{2} | 0.013 |

[&]quot;From Table II adjusted for occupational exposure. Estimated risk to humans from exposure to a time-weighted average of 1 μg/m³ for a normal 8-hour workday, 40-hour workweek, 40-year career (see text).

contains the International Agency for Research on Cancer's (IARC) classification of each of these chemicals.(14) This classification scheme evaluates the likelihood that these chemicals are human carcinogens but makes no attempt to quantify their potential risk or to set "safe" exposure levels. Hexachlorobutadiene is classified by IARC in category 3, "the agent is not classifiable as to its carcinogenicity to humans."(14) Seven other chemicals: acrylamide (2B), acrylonitrile (2A), beryllium (2A), 1,3-butadiene (2B), cadmium (2A), carbon tetrachloride (2B), chloroform (2B), methylene chloride (dichloromethane) (2B), ethylene oxide (2A), and formaldehyde (2A) are in IARC category 2, "the agent is probably (2A) or possibly (2B) carcinogenic to humans." The remaining five chemicals, benzene, bis(chloromethyl) ether, chromium VI, nickel refinery dust (nickel compounds), and vinyl chloride are in IARC category 1 "human carcinogens."

Using vinyl chloride as an example, Figure 2 illustrates the typical relationship found between the dose-response curve resulting from a QRA of the type performed by the EPA, the empirical data on which the modeling is performed, and the TLV established by the ACGIII. The slope of the dose-response curve shown here (i.e., 0.0013) is derived from the EPA unit risk factor for vinyl chloride adjusted to reflect the exposure situation of the occupational environment.

Discussion

In this set of 16 chemicals, both the EPA and the ACGIH approaches rank them in approximately the same order of carcinogenic risk. However, the EPA is far more conservative, reflecting the agency's objective to protect all members of the community, not just healthy adults. The authors could not definitively comment on the relative

accuracy of the two approaches because our theoretical understanding of the dose-response relationship for occupational carcinogens is still elementary, and we are, therefore, limited in our ability to discriminate between the accuracy of the TLV and QRA approaches. One is further hampered by the fact that the empirical data available to assess the carcinogenicity of specific chemicals are usually the result of animal experiments at high doses, together with a battery of short-term tests which are sometimes augmented by epidemiology studies that usually have scanty exposure information. The available occupational cohort studies have not followed workers for their entire lifetime and, thus, do not give complete information on agents which cause cancer many years after exposure. Consequently, no one at the present time can speak with scientific certainty about "safe" levels of exposure to carcinogens.

Although decisions on the permissible exposure to carcinogens are fraught with difficulty, we believe that recommending maximum levels of occupational exposure should be guided by three principles:

- Scientifically, one should seek the most appropriate data and methods for predicting the effect of human exposure to carcinogens based on our latest theoretical understanding of the process of carcinogenesis.
- As a public health issue, one should admit the imprecision of our knowledge and compensate for our uncertainty by building into the system a margin of safety.
- As public policy, one should explicitly document the methodology.

The increasing motivation to use QRA as a tool to establish occupational health standards dates from the 1980 decision by the Supreme Court to overturn the Occupational Safety and Health Administration's (OSHA) newly proposed benzene standard. (15) The court maintained that

OSHA had failed to show a significant reduction in risk going from 10 to 1 ppm. Although OSHA did not propose a formal policy in response to the decision, the agency has generally accepted the view that quantitation of risk is required for the regulation of carcinogens, and it has incorporated QRAs into its standard setting activity since that time.

Amidst the controversy associated with modeling a process the is incompletely understood scientifically and the judicial political climate which favors the use of a quantitative procedure to help regulate carcinogens in the general environment and workplace, the EPA and other regulatory agencies have opted for the use of a conservative approach in the development of risk assessment procedures. For example, the QRAs are usually based on the most sensitive species and use of the most conservative dose-response curve, while low weight is given to negative epidemiological data. (5) Although this procedure has been criticized by some industry representatives(16) and some academic scientists,(17) it would be difficult to perform numerous risk calculations involving all plausible options for the many judgments that must be made in the development of a QRA. For most chemicals, this would result in such a wide range of risk estimates that the analvsis would not be useful to the regulatory agency or to others formulating public policy. The CS-TLV Committee, on the other hand, provides recommendations for the use of industrial hygienists rather than setting governmental standards, and the Committee bases its recommendation on the professional judgement of its members. Both the TLVs and QRAs are subject to external reviews before adoption.

With this perspective in mind, the authors compared the chemical carcinogens which were quantitatively evaluated by the two procedures. The first qualitative comparison is that only 16 chemicals appear on both the CS-TLV Committee list and the EPA list. However, this apparent disagreement is not too surprising because of the substantially different mission of these two organizations and the approaches they take when classifying the hazardous "potency" of chemicals. TLVs are quantitative guidelines for recommended exposures in the workplace, but there is no explicit estimate of the health risk associated with these levels. On the other hand, the EPA unit risk factor explicitly relates dose to cancer risk by means of a mathematical, linearized, multistage model of carcinogenesis, but few have been translated into permissible exposure levels. Operating as an independent organization, the IARC reviews all relevant scientific information in order to assess the evidence that an agent could alter the incidence of cancer in humans but makes no attempt to extrapolate beyond the range of the available data. Likewise, no recommendation is given for safe exposure levels for regulation or legislation.(14)

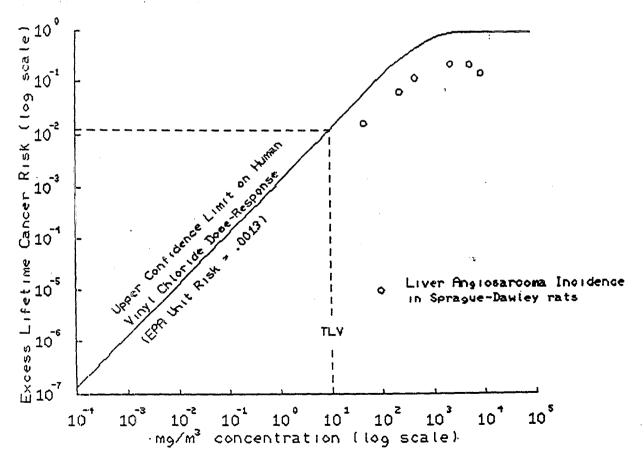


FIGURE 2. Comparison of TLV, EPA unit risk dose-response, and animal bioassay results for vinyl chloride exposure.

The principal reason for this wide disparity between the EPA and the CS-TLV Committee may be explained primarily by the underlying philosophical principles governing the two organizations rather than the technical differences between the two methods. The CS-TLV Committee is governed by the principle that "Threshold limit values refer to airborne concentrations of substances and represent conditions under which it is believed that nearly all workers may be repeatedly exposed day after day without adverse effect. Because of wide variation in individual susceptibility, however, a small percentage of workers may experience discomfort from some substances at concentrations at or below the threshold limit; a smaller percentage may be affected more seriously by aggravation of a pre-existing condition or by development of an occupational illness."(12) Use of the TLV for other purposes, such as community air standards, is specifically discouraged by the Committee. Thus, the CS-TLV Committee recommendations imply that there is a small degree of risk of occupational illness to some workers who are more susceptible than others.

The Clean Air Act, which in part governs EPA's approach to performing QRAs, is more philosophically conservative. The Act states that Primary Air Standards must protect the public health with an adequate margin of safety based on a review of air quality criteria which reflects the latest state of scientific knowledge about the pollutant. The requirement for an "adequate margin of safety" is intended both to address inconclusive scientific and technical information and to provide a reasonable degree of protection against hazards that research has not yet identified. Recognizing that imposing zero emission for some substances would impose too heavy an economic burden on society, EPA has addressed the problem by proposing that the Best Available Technology (BAT) be used to control carcinogens. If BAT controls leave an unreasonable residual risk, further controls will be considered.(17)

When making a quantitative comparison between the ACGIH and the EPA approaches, substantial agreement is found when classifying the relative potencies of these carcinogens, but substantial disparity in the actual levels proposed or recommended. Estimating lifetime cancer risks from occupational exposure at the ACGIH's TLV levels by using the EPA's QRA model sometimes resulted in extraordinarily high risk estimates, 68 percent from exposure to 1,3-butadiene and 19 percent from exposure to chloroform, which may reflect either limitations in the QRA modeling approach or the TLV safety factor approach.

A safety factor approach, such as that used by the CS-TLV Committee, is theoretically no more or less conservative than a QRA approach which is linear at low doses and assumes no threshold. In practice, however, use of a safety factor of 5–10 or even 100–1000 is markedly less conservative than the QRA approach which determines an exposure level associated with a very small risk level such as V_{10} 6. This point is illustrated for vinyl chloride in Figure 2 which compares the EPA unit risk factor for the upper confidence limit on the estimated human dose–response

with the TLV and the results of animal bioassays. With no attempt made to acknowledge the inconsistency produced by these differing methods, confusion and skepticism have resulted. Although there are strengths and weaknesses associated with the approach of each group, it would seem that the CS-TLV Committee could make a major contribution to fostering control of carcinogens in the workplace by reviewing any available EPA QRA, or comparable modeling data when it updates or establishes a new TLV for a confirmed or suspected human carcinogen. When possible, the CS-TLV Committee should also consider the results of studies that use more refined models for QRA. Being less constrained by the judicial-political climate than the regulatory agencies, the CS-TLV Committee should be better able to promptly adopt the most scientifically defensible extrapolation procedures available when a particular chemical is being studied in terms of recommended occupational exposure values.

Although many scientists remain skeptical about the possibility of extrapolating the effects of carcinogens to low doses, a systematic evaluation of the results of these estimates in future editions of the TLV Documentation volume would help alleviate the confusion that now exists.

References

- Spirtas, R.; Steinberg, M.; Wands, R.C.; Weisburger, E.K.: Identification and Classification of Carcinogens Procedures of the Chemical Substances Threshold Limit Value Committee, ACGIH. Am. J. Public Health 76(10):1232–1235 (1985).
- American Conference of Governmental Industrial Hygienists: Threshold Limit Values for Chemical Substances Biological Exposure Indices for 1989–1990. ACGIH, Cincinnati, OH (1989).
- U.S. Environmental Protection Agency: Respondents brief in support of proposed findings, conclusions and order at 63–64, in re. Stevens Industry, Inc. (Consolidated Di)T Hearings), April 5, 1972.
- U.S. Environmental Protection Agency: Respondents motion to determine whether or not the registrations of mirex should be canceled or amended; Attachment A, September 5, 1975.
- U.S. Environmental Protection Agency: Interim Procedures and Guidelines for Health Risk and Economic Impact Assessments of Suspected Carcinogens. Fed. Reg. 41:21402–21405 (1976).
- Office of Science and Technology: Policy on: Chemical Carcinogens; A Review of the Science and Its Associated Principals. Fed. Reg. 50:10372– 10442 (February 1985).
- National Research Council: Risk Assessment in the Federal Government: Managing the Process. National /.cademy Press, Washington DC (1983).
- Castleman, B.I.; Ziem, G.E.: Corporate Influence on Threshold Limit Values. Am. J. Ind. Med. 13:531–559 (1988).
- Andersen, M.E.: Quantitative Risk Assessment and Occupational Carcinogens. Appl. Ind. Hyg. 3(10):267–272 (1988).
- 10. Comfield, J.: Carcinogenic Risk Assessment. Science 198693-699 (1977).
- Moolgavkar, S.H.; Knudson, Jr., A.G.: Mutation and Cancer: A Model for Human Carcinogenesis. J. Natl. Cancer Inst. 66:1037–1052 (1981).
- American Conference of Government Industrial Hygienist: Threshold Limit Values and Biological Exposure Indices for 1967–1968. ACGIH, Cincinnati, OH (1967).
- U.S. Environmental Protection Agency: Integrated Risk Information System. EPA/600/8-86/032a. Office of Health and Environmental Assessment, US Environmental Protection Agency, Washington, DC (1987).
- 14. International Agency for Research on Cancer: Overall Evaluations of Carcinogenicity, Suppl. F. An Updating of IARC Monographs Volumes 1 to 42. IARC, Lyon, France (March 1967).

- Supreme Court of the United States: Industrial Union Department, AFL-CIO v. American Petroleum Institute, et al., argued October 10, 1979, decicled July 2, 1980, No. 78–911. Washington, DC (1980).
- American Industrial Health Council: Comment on: A Report of the Interagency Regulatory Liaison Group Entitled "Scientific Bases for Identifying Potential Carcinogens and Estimating their Risk." AIHC, Scarsdale, NY (May 5, 1979).
- Purchase, I.F.: Inter-species Comparisons of Carcinogenicity. Br. J. Cancer 41:454–468 (1980).
- U.S. Environmental Protection Agency: Policy and Procedures for Identifying, and Assessing and Regulating Airborne Substances Posing a Risk of Cancer. Proposed Rule Fed. Reg. 44:58642 (1980).

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COMMENTARY

Interview with a Risk Expert*

Daniel E. Koshland, Jr.

Science: "Dr. Noitall, you are the ultimate authority on all types of risks, a revered figure who has just appeared on national television."

Noitall: "A vast understatement of my true value."

Science: "You must have a large laboratory to uncover so many facts not available to the regulatory agencies."

Notiall: "Facts are no longer created in laboratories; they are created in the media. Any pronouncement of mine repeated in three periodicals, four newspapers, or one television program is considered a fact. My appearance on three talk shows is enough to qualify me as an expert. It is no longer necessary to have a laboratory in my profession."

Science: "Could you give an example of how to avoid risks?" Noitall: "Stay out of the home. More than 3 million people in the United States were injured in 1987 in home accidents; 90 percent of all automobile accidents occur within 10 miles of home. It is imperative that you stay away from home." Science: "But I've heard that many accidents occur on highways."

Noitall: "That is true. There is one fatality for every 10 minutes of driving on the highways in the United States. I have developed a rigorous formula that shows that the more time spent on the highway, the greater the chance of an accident. Therefore, I recommend driving 80 miles per hour as a way of reducing the time spent on highways and thus reducing your chance of accident.

Science: "If one stays away from home, is there not an increased chance of infectious diseases?"

Noitall: "One has to give up sexual intercourse entirely. The danger of disease from that source is far greater than from eating an apple, and it should be avoided at all costs." Science: "Are there other dangers about which the Environmental Protection Agency has failed to advise us?"

Noitall: "Breathing. All breathing generates oxygen radicals, which are the main sources of mutations in DNA, leading to cancer, birth defects, and very peculiarly shaped molecules in the urine. Breathing has been observed 3 minutes before death in 100 percent of all fatalities. We urge everyone to stop breathing until the proper research has been carried out. The EPA has been told about this relation and has failed to act on it, a scandalous display of irresponsibility."

Science: "What about hazards from crime?"

Noitall: "A third of all homicides are committed on intimates, about a third on acquaintances, and about a third on strangers. Hence, it is imperative to avoid intimates, acquaintances, and strangers in order to reduce your risk of homicide significantly."

Science: "Can one ever completely eliminate a given risk?"

Noitall: "One can reduce a risk to essentially zero by adopting what I call 'the riskier alternative strategy.' For example, one could take up hang gliding, as it has been conclusively demonstrated that fewer hang gliders die of passive cigarette smoke than those who never participate in the sport. People who bicycle without a helmet need not worry about a little nuclear reactor nearby. People who have a cocktail before dinner or wine with a meal need never worry about a little trichloroethylene in their drinking water. By the proper choice of alternative strategies, it is possible to reduce one's chance of dying of any particular disorder to any desired level. It has relieved many people of risk anxiety syndrome."

Science: "This seems so sensible; I am surprised people don't follow your advice."

Noitall: "Most ignoramuses are in fact following my formula without knowing it. Millions of people commute 20 miles to work, take airplanes, and choose hopelessly short-lived grandparents and still worry about clean drinking water. These people are secret admirers of peptic ulcers."

Science: "We can't thank you enough for the time you are spending with us, but I have one last question. Do you practice what you preach?"

Noitall: "Sadly, the answer is no. My family on the paternal side has a hereditary weakness whose clinical manifestation is the 'eat, drink, and be merry' psychosis. As a result, all my ancestors on that side of the family have died prematurely, in their early nineties. I doubt whether I will escape the family curse."

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SCIENCE AND ITS LIMITS: The Regulator's Dilemma

Alvin M. Weinberg

PROLOGUE: The shift in environmental concerns from visible pollution to more subtle threats, such as toxic pollutants, presents special problems for regulators who must function outside the limits of scientific certainty. The same handicap besets judges who must adjudicate disputes over claims for damages arising from new and hazardous technologies that involve adverse health effects that are latent or unpredictable.

In this area of uncertainty in which accidental exposure to hazards is rare, scientists resort to probabilistic risk assessment to estimate the likelihood and consequences of events that may carry a threat to human health. Such scientific techniques for the investigation of rare events, however, often cannot provide definitive answers for regulators and judges.

In this essay physicist Alvin Weinberg suggests that instead of asking scientists for answers to unanswerable questions, regulators should settle for less-definitive answers and regulate on the basis of uncertainty. Technological fixes, including greater reliance on inherent safety features that depend on the immutable laws of nature, can help reduce risk. But ultimately, says Weinberg, it may be necessary to establish some threshold beyond which blame for accidents and other untoward events would be unprovable and victims would be compensated by a society as a whole.'

Alvin M. Weinberg received his Ph.D. in physics from the University of Chicago in 1939. He has been a leading figure in the development of nuclear energy and has served as director of the Oak Ridge National Laboratory and as director of the Institute for Energy Analysis of the Oak Ridge Associated Universities. He is the coauthor of The Physical Theory of Neutron Chain Reaction (1958) and has written extensively on nuclear energy, nuclear proliferation, and the interaction between modern technology and society.

n his essay "Risk, Science, and Democracy," William D. Ruckelshaus expresses very clearly what I call the regulator's dilemma. During the past 15 years. Ruckelshaus notes, there has been a shift in public emphasis from visible and demonstrable pollution problems, such as smog resulting from automobiles and raw sewage, to potential and largely invisible problems, such as the effects of low concentrations of toxic pollutants on human health. This shift is important for two reasons. First, it has changed the way that science is applied to practical questions of public health protection and environmental regulation. Second, it has raised difficult questions about managing chronic risks within the context of free and democratic institutions.²

When the environmental concern was patent and obvious—such as the problem of smog in Los Angeles—science could and did provide unequivocal answers. Smog, for example, comes from the gas emissions from burning liquid hydrocarbons, and the answer to the smog problem lies in controlling these emissions. The regulator's course was rather straightforward because the science upon which regulatory decisions are made was operating well within its power. However, when the environmental concern is subtle—for example, how much cancer is caused by an increase of 10 percent in mean background radiation—science is being asked a question that lies beyond its power; the question is trans-scientific. Yet the regulator, by law, is expected to regulate even though science can hardly help him; this is the regulator's dilemma.

Although my essay is subtitled The Regulator's Dilemma, many of the same issues arise in the adjudication of disputes over who is to blame and who is to be compensated for damage allegedly caused by rare events, such as nuclear accidents. The regulator's dilemma is also faced by the judge who is presiding over a tort case involving, for example, a claim for damages blamed on a toxic waste dump. Indeed, the regulator's dilemma could equally be called the toxic tort dilemma.

A lawsuit involving alleged injury from chemical pollutants is unlike the traditional liability case. If my car injures a pedestrian, I am liable to be sued. What is at issue, however, is not whether I have injured a pedestrian. Rather, it is whether I am at fault. On the other hand, if the lead from my car's exhaust is alleged to cause bodily harm, the issue is not whether my car emitted the lead but whether the lead actually caused the alleged harm. The two situations are quite different. In the first example the relation between cause and injury is not at issue. In the second it is the issue.

In this essay, therefore, I try to delineate more precisely those limits to science that give rise to the regulator's dilemma. I speculate on how these intrinsic limits to science seem to have catalyzed a profound attack on science by some sociologists and public-interest activists. In addition, I offer a few ideas that may help the harried regulators finesse these trans-scientific issues.

II

Science deals with regularities in our experience; art deals with singularities. It is no wonder that science tends to lose its predictive or even explanatory power when the phenomena it deals with are singular,

irreproducible, and one of a kind—in other words, rare. Although science can often analyze a rare event after the fact—for example, the extinction of dinosaurs during the Cretaceous-Tentary period following the presumed collision of the earth and an asteroid—it has great difficulty predicting when such an uncommon event will occur.

I distinguish here between two sorts of rare events—accidents and low-level insults, whose potential to cause injury is unknown. Accidents are large-scale malfunctions whose etiology is not in doubt, but whose likelihood is very small. The partial nuclear reactor meltdown at Three Mile Island in 1979 and the release of toxic gas from a chemical plant at Bhopal, India, in 1984 are examples of accidents. The precursors to these specific events—for example, the condition of the auxiliary water feed system and other components at Three Mile Island—and the way in which the accidents unfolded are well understood. Estimates of the likelihood of the particular sequence of malfunctions are less firmly grounded. As the number of individual accidents increases, prediction of their probability becomes more and more reliable. We can predict very well how many automobile fatalities will occur in 1986; we can hardly claim the same degree of reliability in predicting the number of serious reactor accidents in 1986.

Low-level insults are rare in a rather different sense. We know that about 100 rems of radiation will double the mutation rate in a large population of exposed mice. How many mutations will occur in a population of mice exposed to 100 millirems of radiation? In this case the mutations, if induced at all by such low levels of exposure, are so rare that to demonstrate an effect with 95 percent confidence would require the examination of many millions of mice. Although such an effort is not impossible in principle, it is in practice. Moreover, even if we could perform so heroic a mouse experiment, the extrapolation of these findings to humans would still be fraught with uncertainty. Thus, human injury or abuse from low-level exposure to radiation is a rare event whose frequency cannot be accurately predicted.

Ш

When dealing with events of this sort, science resorts to the language of probability. Instead of saying that this accident will happen on that date, or that a particular person exposed to a low-level dose of radiation will suffer a particular fate, it tries to assign probabilities for such occurrences. Of course, where the number of instances is very large or the underlying mechanisms are fully understood, the probabilities are themselves perfectly reliable. In quantum mechanics there is no uncertainty as to the probability distribution of the phenomenon being described. In the class of phenomena considered here, however, even though the likelihood of an event happening or of a disease being caused by a specific exposure is given as a probability, the probability itself is very uncertain. One can think of a somewhat fuzzy demarcation between what I have called science and trans-science. The domain of science covers phenomena that are deterministic or whose probability of occurrence can itself be stated precisely; in contrast, trans-science covers those events whose probability of occurrence is itself highly uncertain.

Although science can often analyze a rare event after the fact, it has great difficulty predicting when such an uncommon event will occur.

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Despite the difficulties, scientific mechanisms have been devised for estimating, however imperfectly, the probability of rare events. For accidents the technique is probabilistic risk assessment (PRA); for low-level insults various empirical and theoretical approaches are used.

Although probabilistic risk assessment had been used in the aerospace industry for a long time (for example, to predict the reliability of components), it first sprang into public prominence in 1975 with a reactor safety study directed by nuclear engineer Norman C. Rasmussen.³ The Rasmussen study, sponsored by the Atomic Energy Commission (now known as the Nuclear Regulatory Commission), was designed to estimate the public risks involved in potential accidents at commercial nuclear reactors.

Probabilistic risk assessment, when applied to nuclear reactors, seeks to identify all sequences of subsystem failures that may lead to a failure of the overall system; it then tries to estimate the consequences of each subsystem failure so identified. The result is a probability distribution, P(C); that is, the probability, P, per reactor year, of a consequence having magnitude C. Consequences include both material damage and health effects. Usually, the probability of accidents having large consequences is less than the probability of accidents having small consequences.

A probabilistic risk assessment for a reactor requires two separate estimates: first, an estimate of the probability of each accident sequence; second, an estimate of the consequences—particularly the damage to human health—caused by the uncontrolled radioactive effluents released in the accident. An accident sequence is a series of equipment or human malfunctions, such as a pump that fails to start, a valve that does not close, or an operator confusing an ON with an OFF signal. We have statistical data for many of these individual events; for example, enough valves have operated for enough years so that we can, at least in principle, make pretty good estimates of the probability of failure.

Uncertainties still remain, however, because we can never be certain that we have identified every relevant sequence. Proof of the adequacy of probabilistic risk assessment must therefore await the accumulation of operating experience. For example, the median probability of a core melt in a light water reactor, according to the 1975 Rasmussen study, was 1 in every 20,000 reactor-years; the core melt at Three Mile Island's number two reactor (TMI-2) occurred after only 700 reactor-years. The number two reactor, however, differed from the reactors Rasmussen studied, and in retrospect, one could rationalize most of the discrepancy between his estimate and the seemingly premature occurrence at TMI-2.

Since the core melt at Three Mile Island, the world's light water reactors have accumulated some 1,500 reactor-years of operation without a core melt. This performance places an upper limit on the a priori estimate of the coremelt probability. Thus, if this probability were as high as 1 in every 1,000 reactor years, the likelihood of surviving 1,500 reactor-years would not be more than 22 percent; put otherwise, we can say with 78 percent confidence that the core-melt probability is not as high as 1 in 1,000 reactor years. With 500 light water reactors on line in the world, should we survive until the year 2000 without another core melt, we could then say with 95 percent confidence

As we see, after 3,000 reactor-years of operation without a core melt, we can say with about 78 percent confidence that Rasmussen's upper limit (1 in 2,000 reactor-years) is not too optimistic. Furthermore, if we survive to the year 2000 without a core melt, the confidence level with which we can make this assertion rises to 95 percent. Our confidence in probabilistic risk assessment can eventually be tested against actual, observable experience. Until this experience has been accumulated, however, we must concede that any probability we predict must be highly uncertain. To this degree our science is incapable of dealing with rare accidents, but time, so to speak, annihilates uncertainty in estimates of accident probability.

Unfortunately, time does not annihilate uncertainties over consequences as unequivocally as it does uncertainties over frequency of accidents. A large reactor or chemical plant accident can cause both immediate, acute health effects and delayed, chronic effects. If the exposure either to radiation or to methyl isocyanate is high enough, the effect on health is quite certain. For example, a single exposure of about 400 rems will cause about half of the people exposed to die. On the other hand, in a large accident many people will also be exposed to smaller doses—indeed, to doses so low that the resulting health effects are undetectable. At Bhopal many thousands of people were exposed to methyl isocyanate but they recovered. We cannot say positively whether or not they will suffer some chronic disability.

The very worst accident envisaged in the Rasmussen study, with a probability of 1 in 1 billion reactor-years, projected an estimated 3,300 early fatalities, 45,000 early illnesses, and 1,500 delayed cancers per year among 10 million exposed people. Almost all of the estimated delayed cancers are attributed to exposures of less than 1,000 millirems per year—a level at which we are very hard put to estimate the risk of inducing cancer. Similarly, the American Physical Society's critique of the Rasmussen study attributed an additional 10,000 deaths over 30 years among 10 million people exposed to cesium-135 distributed in a very large accident. The average exposure in this case was assumed to be 250 millirems per year—again, a level at which our estimates of the health effects are extremely uncertain.

Has the nuclear community, particularly its regulators, figuratively shot itself in the foot by trying to estimate the number of delayed casualties as a result of these low-level exposures? In retrospect, I think the Rasmussen study would have been on more solid ground had it confined its estimates to those health effects resulting from exposures at higher levels, where science makes reliable estimates. For the lower exposures the consequences could have been stated simply as the number of man-rems (the number of people multiplied by the number of rems) of exposure of individuals whose total exposure did not exceed, say, 5,000 millirems, without trying to convert this man-rems number

Our confidence in probabilistic risk assessment can eventually be tested against actual, observable experience.

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into numbers of latent cancers. Thus, health consequence would be reported in two categories: (1) for highly exposed individuals, the number of health effects; and (2) for slightly exposed individuals, the total man-rems or even the distribution of exposures accrued by the large number of individuals so exposed. Perhaps such a scheme could be adopted in reporting the results of future probabilistic risk assessments; at least it has the virtue of being more faithful than the present convention to the state of scientific knowledge

IV

In both of my examples of accidents (Bhopal and nuclear accidents), many people are exposed to low-level insult. The uncertainties inherent in estimating the effects of such low-level exposure are heaped on top of the uncertainties in estimating the probability of the accident that may lead to exposure in the first place.

Science has exerted great effort to ascertain the shape of the doseresponse curve at low dose—but very little, if anything, can be said with certainty about the low-dose response. Thus, to quote the report of the National Research Council, The Effects on Populations of Exposure to Low Levels of Ionizing Radiation: 1980 (also known as BEIR-III, for the committee that prepared it, the Committee on the Biological Effects of Ionizing Radiation), "The Committee does not know whether dose rates of gamma or x-rays of about 100 mrads/yr are detrimental to man.... It is unlikely that carcinogenic and teratogenic effects of doses of low-LET radiation administered at this dose rate will be demonstrable in the foreseeable future."6 This prompted Philip Handler, then president of the National Academy of Sciences, to comment in his letter of transmittal to the Environmental Protection Agency, which had requested the study, "It is not unusual for scientists to disagree ... (and) ... the sparser and less reliable the data base, the more opportunity for disagreement.... The report has been delayed... to permit time... to display all of the valid opinions rather than distribute a report that might create the false impression of a clear consensus where none exists."

This forthright admission that science can say little about low-level insults I find admirable. It represents an improvement over the unjustified assertion in the BEIR-II report of 1972 that 170 millirems per year over 30 years, if imposed on the entire U.S. population, would cause between 3,000 and 15,000 cancer deaths per year. Ido not quarrel with the estimated upper limit—which amounts to 1 cancer per 2,500 man-rems, but I regard placing the lower limit at 3,000 rather than at zero as unjustified. Moreover, I think it has caused great harm. The proper statement should have been that at 170 millirems per year, we estimate the upper limit for the number of cancers to be 15,000 per year; the lower limit may be zero.

Since the appearance of the BEIR reports, two other developments have added to the burden of those who must judge the carcinogenic hazard of low-level insults: an awareness and study of (1) natural carcinogens, and (2) ambiguous carcinogens.

Natural carcinogens. Is cancer environmental in the sense of being caused by technology's effluents, or is it a natural consequence of aging? In the

etiology for cancer, today the view that natural carcinogens are far more important than are manmade ones has gained many converts. In his 1983 article in Science, biochemist Bruce N. Ames marshaled powerful evidence that many of our most common foods contain naturally occurring carcinogens. Indeed, biochemist John R. Totter, former director of the Atomic Energy Commission's division of biology and medicine, has offered evidence for the oxygen radical theory of carcinogenesis: that we eventually get cancer because we metabolize oxygen and subsequently produce oxygen radicals that can play havoc with our DNA. As such views of the etiology of cancer acquire scientific support, I think that the trans-scientific question, as to how much cancer is caused by a tiny chemical or physical insult will be recognized as irrelevant. One does not swat gnats when pursued by elephants.

Ambiguous carcinogens. To further complicate the cancer picture, there is evidence that some agents, such as dioxin, various dyes, and even moderate levels of radiation, seem to diminish the incidence of some cancers while simultaneously increasing the incidence of others. The lifespan of the animals

past few years we have seen a remarkable shift in viewpoint; whereas 15 years ago most cancer experts would have accepted a primarily environmental

Ambiguous carcinogens. To further complicate the cancer picture, there is evidence that some agents, such as dioxin, various dyes, and even moderate levels of radiation, seem to diminish the incidence of some cancers while simultaneously increasing the incidence of others. The lifespan of the animals exposed to these agents in laboratory tests on average exceeds that of animals not exposed. A most striking example, given by biostatistician Joseph K. Haseman, is yellow dye number 14 given to leukemia-prone female rats. This dye completely suppresses leukemia, which is always fatal, but causes liver tumors, most of which are benign.

I mention these two findings—or perhaps they should be considered points of view—to stress my underlying point: that when we are concerned with low-level insult to human beings, we can say very little about the cancer dose-response curve. Saying that so many cancers will be caused by so much low-level exposure to so many people, a practice that terrifies many people, goes far beyond what science actually can say.

V

Does the scientific community accept the notion that there are intrinsic limits to what it can say about rare events; that as events become rarer, the uncertainty in the probability of occurrence of a rare event is bound to grow? Perhaps a better way of framing this question is: Of what use can we put scientific tools of investigation of rare events, such as probabilistic risk assessment and large-scale animal experiments, if we concede that we can never get definitive answers?

I believe that probabilistic risk assessment with an uncertainty factor as high as 10 is often useful, especially if one uses the technique for comparing risks. For example, the 1,500 reactor-years already experienced since the Three Mile Island accident suggest that a reactor core-melt probability is likely to be less than 1 in 1,000 reactor-years and may well be as low as less than 1 in 10,000 reactor-years. This is to be compared with dam failures whose probability, based on many hundreds of thousands of dam-years (where time has annihilated uncertainty), is around 1 in 10,000 dam-years. Even with an uncertainty factor of 10, we can judge how safe reactors are compared to dams.

Some agents, such as dioxin, various dyes, and even moderate levels of radiation, seem to diminish the incidence of some cancers while simultaneously increasing the incidence of others.

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When one compares the relative intrinsic safety of two very similar devices—such as two water-moderated reactors—probabilistic risk assessment is on much more solid ground. Here one is not asking for absolute estimates of risk, but rather for estimates of relative safety. If reactors A and B differ in only a few details—say reactor A has two auxiliary water feed trains whereas B has only one—the ratio of core-melt probabilities should be much more reliable than their absolute values because the ratio requires an estimate of failure of a single subsystem, in this instance the extra auxiliary water feed on reactor A.

Not only can one say with reasonable assurance how much safer reactor A is than reactor B, but as a result of the detailed analysis one can identify the subsystems that contribute most to the estimated failure rate. Even if probabilistic risk assessment is inaccurate, it is very useful in unearthing deficiencies; one can hardly deny that a reactor in which deficiencies revealed by probabilistic risk assessment have been corrected is safer than one in which they have not been corrected, even if one is unwilling to say how much safer.

Somewhat the same considerations apply to low-level insult. An agent that does not shorten lifespan at high dose will not shorten lifespan at low dose. An agent that is a very powerful carcinogen at high dose is more likely to be a carcinogen at low dose than one that is a less powerful high-dose carcinogen. Thus, animal experiments surely are useful in deciding which agents to worry about and which not to worry about. Of course, the Ames test (which determines by a relatively simple procedure whether a substance is mutagenic) has made at least some preliminary screening of carcinogens more feasible because substances that cause mutations are considered to be potential carcinogens. The difficulty today seems to be not so much identifying agents that at high dose may be carcinogens as it is prohibiting exposures far below levels at which no effect can be, or perhaps ever will be, demonstrated. The regulator and the concerned citizen are inclined to approve the Delaney clause of the Federal Food, Drug, and Cosmetic Act, which prohibits the use of any food additive that has been shown to cause cancer in laboratory animals or humans. This clause, however, is of no help in resolving such issues as the relative risks of, say, cancer induction by nitrosamines (carcinogenic compounds that can be formed in the body from nitrites) and digestive disorders caused by meat untreated with nitrites.

The Delaney clause is the worst example of how a disregard of an intrinsic limit of science can lead to bad policy by overenthusiastic politicians. Harvard physicist Harvey Brooks has often pointed out that one can never prove the impossibility of an event that is not forbidden by a law of nature. Most will agree that a perpetual motion machine is impossible because it violates the laws of thermodynamics. That one molecule of a polychlorinated biphenyl (PCB) may cause a cancer in humans is a proposition that violates no law of nature: hence many, even within the scientific community, seem willing to believe that this possibility is something to worry about. It was this error that led to the Delaney clause.

When is an event so rare that the prediction of its occurrence forever lies outside the domain of science and therefore within the domain of transscience? Clearly we cannot say, and perhaps as science progresses, this

The Delaney clause is the worst example of how a disregard of an intrinsic limit of science can lead to bad policy by overenthusiastic politicians.

boundary between science and trans-science will recede toward events of lower frequency. At any stage, however, the boundary is fuzzy, and much scientific controversy boils over deciding where it lies. One need only read the violent exchange between Edward P. Radford and Harald H. Rossi over the risk of cancer from low levels of radiation to recognize that where the facts are obscure, argument—even ad hominem argument—blossoms. 12 Indeed, Alice Whittemore in her "Facts and Values in Risk Analysis for Environmental Toxicants," has pointed out that facts and values are always intermingled at this "rare event" boundary between science and trans-science. 13 A scientist who believes that nuclear energy is evil because it inevitably leads to proliferation of nuclear weapons (which is a common basis for opposition to nuclear energy) is likely to judge the data on induction of leukemia from low-level exposures at Nagasaki differently than is a scientist whose whole career has been devoted to making nuclear power work. Cognitive dissonance is all but unavoidable when the data are ambiguous and the social and political stakes are high.

VI

No one would dispute that judgments of scientific truth are much affected by the scientist's value system when the issues are at or close to the boundary between science and trans-science. On the other hand, as the matter under dispute approaches the domain of science, most would claim that the scientist's extrascientific values intrude less and less. Soviet scientists and U.S. scientists may disagree on the effectiveness of a ballistic missile defense, but they agree on the cross section of U²³⁵ or the lifetime of the pi meson.

This all seems obvious, even trite. Yet in the past decade or so a school of sociology of knowledge has sprung up in Great Britain that claims that "scientific views are determined by social (external) conditions, rather than by the internal logic of scientific tradition and inherent characteristics of the phenomenal world," or that "all knowledge and knowledge claims are to be treated as being socially constructed: genesis, acceptance, and rejection of knowledge [is] sought in the domain of the Social World rather than . . . the Natural World." 15

The attack here is not on science at the boundary with trans-science, in particular—the prediction of the frequency of rare events. At least the more extreme of the sociologists of knowledge claim that using traditional ways of establishing scientific truth—by appealing to nature in a disciplined manner—is not how science really works. Scientists are seen as competitors for prestige, pay, and power, and it is the interplay among these conflicting aspirations, not the working of some underlying scientific ethic, that defines scientific truth. To be sure, these attitudes toward science are not widely held by practicing scientists; however, they are taken seriously by many political activists who, though not in the mainstream of science, nevertheless exert important influence on other institutions—the press, the media, the courts—that ultimately influence public attitudes toward science and its technologies.

If one takes such a caricature of science seriously, how can one trust a scientific expert? If scientific truth, even at the core of science, is decided by

negotiation between individuals in conflict because they hold different non-scientific beliefs, how can one say that this scientist's opinion is preferable to that one's? Furthermore, if the matter at issue moves across the boundary between science and trans-science, where all we can say with certainty is that uncertainties are very large, how much less able are we to distinguish between the expert and the charlatan, between the scientist who tries to adhere to the usual norms of scientific behavior and the scientist who suppresses facts that conflict with his political, social, or moral preconceptions?

One way to deal with these assaults on scientists and scientific truth would be to define a new branch of science, called regulatory science, in which the norms of scientific proof are less demanding than are the norms in ordinary science. I should think that a far more honest and straightforward way of dealing with the intrinsic inability of science to predict the occurrence of rare events is to concede this limitation and not to ask of science or scientists more than they are capable of providing. Instead of asking science for answers to unanswerable questions, regulators should be content with less far-reaching answers. For example, where the ranges of uncertainty can be established, regulate on the basis of uncertainty; where the ranges of uncertainty are so wide as to be meaningless, recast the question so that regulation does not depend on answers to the unanswerable. Furthermore, because these same limits apply to litigation, the legal system should recognize, much more explicitly than it has, that science and scientists often have little to say, probably much less than some scientific activists would admit.

The expertise of scientific adversaries is often at the heart of litigation over personal injury alleged to be caused by subtle, low-level exposures. Each side presents witnesses whose scientific credentials it regards as impeccable. Because the issues themselves tend to be trans-scientific, one can hardly decide the validity of the assertions of either side's witnesses. Under the circumstances, I suppose, one is justified in regarding a scientific witness no differently than any other witness; his credibility is judged by his past record, behavior, and general demeanor, as well as the self-consistency of his testimony. Such, at least, was the way in which a federal district court judge, Patrick Kelley, settled *Johnston v. United States*, in which the issue was the claim that exposure to radiation from reworking old aircraft instrument dials had caused injury; Kelley impugned, on grounds no different from those one would invoke in an ordinary lawsuit, the competence if not the integrity of some of the plaintiff's scientific witnesses.

VII

There are various ways to provide some assurance of safety despite uncertainty. Here I briefly describe two of these ways—which I call the technological fix and de minimis—without claiming that these are the most important, let alone the only, ones.

Technological fix. Science cannot exactly predict the probability of a serious accident in a light water reactor or the likelihood that a radioactive waste canister in a depository will dissolve and release radioactivity to the environment. Can one design reactors or waste canisters for which the

Instead of asking science for answers to unanswerable questions, regulators should be content with less far-reaching answers.

probability of such occurrences is zero—or at least, where the prevention of such mishaps relies on immutable laws of nature that can never fail rather than on the less than reliable intervention of electromechanical devices? Surprisingly, this approach to nuclear safety has come into prominence only in the past five years. Kare Hannerz in Sweden and Herbert Reutler and Günter H. Lohnert in West Germany have proposed reactor systems whose safety does not depend on active interventions, but rather on passive, inherent characteristics. 16 Although one cannot say that the probability of mischance has been reduced to zero, there is little doubt that the probabilities are several, perhaps three, orders of magnitude lower than the probabilities of mischance for existing reactors. To the extent that such proposed reactors embody the principle of inherent safety, their adoption would avoid much of the dispute over reactor safety, the limits on nuclear accident liability contained in the Price-Anderson Act, repetition of the Three Mile Island accident, and so forth. In short, such a technological fix enables one largely to ignore the uncertainties in any prediction of core-melt probabilities.

The idea of incorporating inherent or passive safety into the design of chemical plants had been proposed by Trevor A. Kletz of the Loughborough University of Technology in 1974, shortly after the disaster at the Flixborough cyclohexane plant, which killed 28 people.¹⁷ I suspect that one of the main consequences of the Bhopal disaster will be the incorporation of inherent safety features into new chemical plants; again, a way of finessing uncertainty in predicting failure probabilities.

De minimis. A perfect technological fix, such as a totally safe reactor or a crash-proof car, is usually not available, at least at an affordable cost. Some low-level exposure to materials that are toxic at high levels is inevitable, even though we can never accurately establish the risk of such exposure. One way of dealing with this situation is to invoke the principle of de minimis. This principle, as Howard I. Adler and I suggested several years ago, argues that for insults that occur naturally and to which the biosphere has always been exposed and presumably to which it has adapted, one should not worry about any additional man-made exposure as long as the man-made exposure is small compared to the natural exposure.¹⁸ The basic idea is that the natural level of a ubiquitous exposure (such as cosmic radiation), if it is deleterious. cannot have been very deleterious because in spite of its ubiquity, humans have survived. Moreover, we do not know and can never know what the residual effect of that natural exposure really is. An additional exposure that is small compared to natural background radiation should be acceptable; at the very least, its deleterious effect, if any, cannot be determined.

Adler and I suggested that for radiation whose natural background is well known, one may choose a de minimis level as the standard deviation of the natural background. This turns out to be around 20 percent of the mean background, around 20 millirems per year; this value has been used as the Environmental Protection Agency standard for exposure to the entire radiochemical fuel cycle.

Scientists know more about the natural incidence and biological effects of radiation than they do about any other agent. It would be natural, therefore, to use the standard established for radiation as a standard for other agents.

This approach has been used by chemist T. Westermark of the Royal Institute of Technology in Stockholm. He has suggested that for naturally occurring carcinogens such as arsenic, chromium, and beryllium, one may choose a de minimis level to be, say, 10 percent of the natural background.¹⁹

Clearly, a de minimis level will always be somewhat arbitrary. Nevertheless, it seems to me that unless such a level is established, we shall forever be involved in fruitless arguments, the only beneficiaries of which will be the toxic tort lawyers. Could the principle of de minimis be applied in litigation in much the same way it may be applied to regulation—that is, if the exposure is below de minimis, then the blame is intrinsically unprovable and cannot be litigated? I would imagine that the legal de minimis may be set higher than the regulatory de minimis; for example, the legal de minimis for radiation could be the background (after all, the BEIR-III committee concedes there is no way of knowing whether or not such levels are deleterious). The regulatory de minimis could justifiably be lower, simply on grounds of erring on the side of safety.

One approach may be to concede that there is some level of exposure that is beyond demonstrable effect. This defines a trans-scientific threshold. A de minimis level could then be established at some fraction, say one-tenth, of this beyond-demonstrable-effect level. For example, if we take 100 millirems per year of radiation as the beyond-demonstrable-effect level for general somatic effects (damaging somatic cells as opposed to germline cells), which is the value according to the BEIR-III committee, a de minimis level could be set at 10 millirems per year. Of course, such a procedure would evoke much controversy as to what is the beyond-demonstrable-effect level or whether 10 is an ample safety factor. This example demonstrates, however, that at least in the case of low-level radiation, a scientific committee has been able to agree on a beyond-demonstrable-effect level. As for the safety factor of 10, this cannot be adjudicated on scientific grounds. The most one can say is that tradition often supports a safety factor of 10—for example, the old standard for public exposure (500 millirems per year) was set at one-tenth of the tolerance level for workers (5,000 millirems per year).

Can the principle of de minimis be applied to accidents? What I have in mind is the notion that accidents that are sufficiently rare may be regarded somehow in the same category as acts of God and be compensated accordingly. We already recognize that natural disasters should be compensated by the society as a whole. One can argue that an accident whose occurrence requires an exceedingly unlikely sequence of untoward events may also be regarded as an act of God. Thus, the Price-Anderson Act could be modified so that, quite explicitly, accidents whose consequences exceeded a certain level, and whose probability as estimated by probabilistic risk assessment would be less than, say, 1 in 1 billion per year, would be treated as acts of God. Compensation in excess of the amount stipulated in the revised act would be the responsibility of Congress. The cutoff for either compensation or for probabilities would be negotiable, and perhaps it would be revised every 10 years or so. One not entirely fanciful suggestion may be to set any probability of the order of 1 in 10 million to 1 in 100 million per year to be a de minimis cutoff, this being the frequency at which the earth may have been visited by

One can argue that an accident whose occurrence requires an exceedingly unlikely sequence of untoward events may also be regarded as an act of God.

the cometary asteroids that may have caused the extinction of species in past geologic eras.

VIII

As in most such questions, identifying and characterizing the problem is easier than solving it. That the dilemma of the regulator and the toxic tort judge is rooted in science's inability to predict rare events cannot be denied. Getting the regulator and the toxic tort judge off the horns of the dilemma is far from easy, and my two suggestions—the technological fix and de minimis—are offered tentatively and with diffidence.

Equally obvious is the intrinsic social dimension of the issue. In an open, litigious democracy such as ours, any regulation and any judicial decision can be appealed, and if the courts offer no redress, Congress, in principle, can do so. These legal mechanisms are ponderous, however. The result seems to me to be a gradual slowing of our technological-social engine as we become more and more enmeshed in fruitless argument over unresolvable questions.

Western society was debilitated once before by such fruitless tilting with Don Quixotian windmills. I refer of course to the devastating campaign against witches from the fourteenth century to the early seventeenth century. As ecologist William Clark has put it so vividly, society took it for granted during that period that death, disease, and crop failure could be caused by witches. To avoid such catastrophes, one had to burn the witches responsible for them—and consequently some million innocent people were burned. Finally, in 1610, the Spanish inquisitor Alonzo Salazar y Frias realized there was no demonstrated connection between catastrophe and witches. Although he did not prohibit the burning of witches, he did prohibit use of torture to extract confessions. The burning of witches, and witch hunting generally, declined precipitously.

I have recounted this story many times by now. Yet it still seems to me to capture the essence of our dilemma: the connection between low-level insult and bodily harm is probably as difficult to prove as the connection between witches and failed crops. I regard it as an aberration that our society has allowed this issue to emerge as a serious social concern, which in the modern context is hardly less fatuous than were the witch hunts of the past. That dark phase in western society died out only after several centuries. I hope our open, democratic society can regain its sense of proportion far sooner and can get on with managing the many real problems we always will face rather than waste its energies on essentially insoluble, and by comparison, intrinsically unimportant, problems.

NOTES:

- 1. This article was adapted from a paper delivered at a June 3-4, 1985, National Academy of Engineering symposium on "Hazards: Technology and Fairness." A report on that symposium will be published in book form by the National Academy Press.
- William D. Ruckelshaus, "Risk, Science, and Democracy," Issues in Science and Technology I (Spring 1985): 19-38.
- U.S. Nuclear Regulatory Commission, Reactor Safety Study: An Assessment of Accident Risk in U.S. Commercial Nuclear Plants (WASH-1400, NUREG 75/014) (Washington, D.C., 1975).

2025545711

- U.S. Nuclear Regulatory Commission, Risk Assessment Review Group Report to the U.S. Nuclear Regulatory Commission (NUREG/CR-0400) (Washington, D.C., September 1978), vi.
- "Report to the American Physical Society by the Study Group on Light Water Reactor Safety," Reviews of Modern Physics 47 (Supplement 1) (Summer 1975).
- 6. National Research Council, The Effects on Populations of Exposure to Low Levels of Ionizing Radiation: 1980 (BEIR-III), (Washington, D.C.: National Academy Press, 1980), 2.
- 7. National Research Council, The Effects on Populations of Exposure to Low Levels of Ionizing Radiation: 1980 (BEIR-III), iii.
- 8. National Research Council, The Effects on Populations of Exposure to Low Levels of Ionizing Radiation (BEIR-II), (Washington, D.C.: National Academy Press, 1972), 2.
- Bruce N. Ames, "Dietary Carcinogens and Anticarcinogens," Science 221 (Sept. 23, 1983): 1249, 1256-64.
- John R. Totter, "Spontaneous Cancer and Its Possible Relationship to Oxygen Metabolism," Proceedings of the National Academy of Sciences 77 (April 1980): 1763-67.
- Alvin M. Weinberg and John B. Storer, "On 'Ambiguous' Carcinogens and Their Regulation," Risk Analysis 5 (June 1985): 151-55.
- 12. National Research Council, The Effects on Populations of Exposure to Low Levels of Ionizing Radiation: 1980 (BEIR-III), 287-321.
- 13. Alice Whittemore, "Facts and Values in Risk Analysis for Environmental Toxicants," Risk Analysis 3 (March 1983): 23-33.
- 14. John Ben-David, "Emergence of National Traditions in the Sociology of Science: The United States and Great Britain," Sociological Inquiry 48, nos. 3 and 4 (1978): 209.
- Trevor J. Pinch and Wiebe E. Bijker, "The Social Construction of Facts and Artefacts: Or How the Sociology of Science and the Sociology of Technology Might Benefit Each Other," Social Studies of Science 14 (1984): 401.
- Kåre Hannerz, Towards Intrinsically Safe Light Water Reactors (ORAU/IEA-83-2(M) Rev.) (Oak Ridge, Tenn.: Oak Ridge Associated Universities, Institute for Energy Analysis, June 1983); Herbert Reutler and Günter H. Lohnert, "The Modular High Temperature Reactor," Nuclear Technology 62 (July 1983): 22-30.
- 17. Trevor A. Kletz. Cheaper. Safer Plants or Wealth and Safety at Work: Notes on Inherently Safer and Simpler Plants (Rugby, England: The Institution of Chemical Engineers, 1984).
- Howard I. Adler and Alvin M. Weinberg, "An Approach to Setting Radiation Standards," Health Physics 34 (June 1978): 719–20.
- 19. T. Westermark, Persistent Genotoxic Wastes: An Attempt at a Risk Assessment (Stockholm: Royal Institute of Technology, 1980).
- William C. Clark, Witches, Floods, and Wonder Drugs: Historical Perspectives on Risk Management (RR-81-3) (Laxenburg, Austria: International Institute for Applied Systems Analysis, March 1981).

Introduction to Risk Analysis

Wilson

RISK/BENEFIT ANALYSIS

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The importance of perceptions of risks is illustrated by Table 1-1. which summarizes results of a public opinion survey. Most people seem to believe that life is becoming more dangerous, even though most objective measures show the contrary to be true. The expectation of life, for example, an inverse measure of the probability of dying, has steadily increased, from perhaps twenty-eight years fifteen centuries ago, to fifty years one century ago, to about seventy-two years currently, although the rate of increase has been decreasing. The increase has been brought about by the elimination of many large risks to life, among them many infectious and contagious diseases, poor working conditions, and inadequate nutrition. Figure 1-1 shows the reduction in death rates in this century by age group. Detailed examination shows that the increase since 1960 in the 15 to 24 age group is due to automobile accidents. Doll (1979) has also shown how health, as measured by most medical indicators, is improving. It is now necessary to concentrate on the many smaller risks, often poorly understood, in order to further reduce total risks. Perhaps it is

Table 1-1. Public Opinion Survey Comparing Risk Today to Risk of Twenty Years Ago.

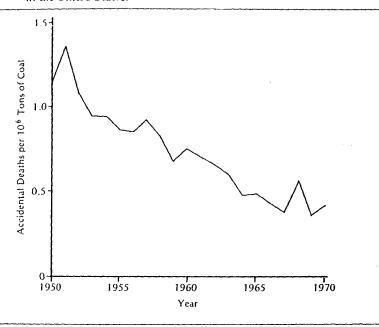
Q: Thinking about the actual amount of risk facing our society, would you say that people are subject to more risk today than they were twenty years ago, less risk today, or about the same amount of risk today as twenty years ago?

Q: I'd like to start by asking you a few questions about the amount of risk we face in our day-to-day living. Thinking about the actual amount of risk facing our society, would you say people are subject to more risk today than the \(\gamma \) were twenty years ago, less risk today, or about the same amount of risk today as twenty years ago?

| | Top Corporate Executives (N = 401) | Investors, Lenders (N = 104) | Congress (N = 47) | Federal Regulators (N = 47) | Public (N = 1,488) |
|-------------|---|------------------------------------|----------------------|-----------------------------------|-----------------------|
| | | | (percent) | | |
| More risk | 38 | 60 | 55 | 43 | · 78 |
| Less risk | 36 | 13 | 26 | 13 | 6 |
| Same amount | 24 | 26 | 19 | 40 | 14 |
| Not sure | 1 | 1 | • • • | 4 | 2 |

Source: Marsh & McLennan Companies (1980).

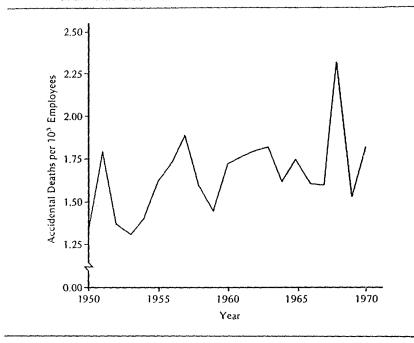
Figure 2-1. Accidental Deaths per Million Tons of Coal Mined in the United States.



What measures of risk are appropriate for a particular risk assessment depend on the specific details of the question the assessment is designed to illuminate. Presumably they will be the measures corresponding as nearly as possible to the way in which the risks are perceived. In what follows we will usually be limiting consideration to risks of death (measured by probabilities of dying or expected excess numbers of deaths) resulting from various actions, although other risks will occasionally be mentioned.

Although we shall not concern ourselves much with it, the distinction between risks and measures of risk is not totally academic. A simple example is the American coal industry, taken as a whole, between 1950 and 1970. Figure 2-1 is a plot of one measure of risk in this industry—the number of accidental deaths per million tons of coal mined. Clearly this measure steadily declined during this period, so that, if we follow the industry through successive years, it appears to be getting safer. Looking at Figure 2-2, which shows the behavior of another measure of risk—the number of accidental deaths per

Figure 2-2. Accidental Deaths per Thousand Coal Mine Employees in the United States.

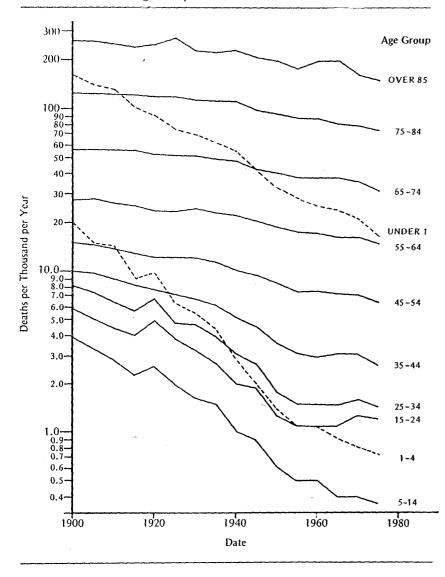


thousand persons employed—one might naively assert that the industry is getting more dangerous, not safer.

Evidently the two measures illustrated might be used to support opposing views on the safety of coal mining. Neither measure taken alone is right or wrong, nor are they even contradictory even though they may be so perceived. Any risk assessment supposed to be complete would have to draw attention to the two aspects of the risk of coal mining gauged by the two different measures and would have to take both into account, depending exactly on the purpose of the risk assessment. From a national point of view, given that a certain amount of coal has to be obtained, deaths per million tons of coal is the more appropriate measure of risk, whereas from a labor leader's point of view, deaths per thousand persons employed may be more relevant.

What steps to take to reduce the risk will depend on which of the two measures is used. Doubling the number of miners, each working

Figure 1-1. Death Rates at Five Year Intervals from 1900 to 1975 for Various Age Groups: United States.

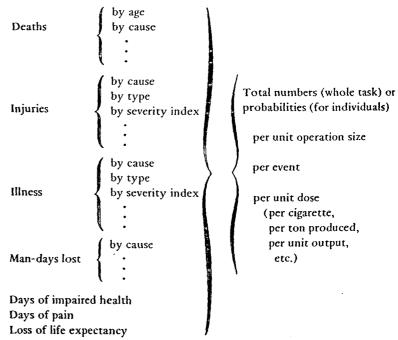


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mum from some point of view. One attempt at reducing such possibilities is the objective analysis of risk, which is pursued throughout this book.

To make any start on objective assessment it is necessary to realize what is being measured. Death is one clear objective measure. The total annual risk of death at any age is just the probability of dying within one year. In the absence of any extra causes, population averages for this measure are obtained from national mortality tables (see Chapter 7). But in risk assessments we are interested in additional risks of death or components of the total risk of death due to some specific actions undertaken either voluntarily or involuntarily. More often, we are interested in how much of an action to undertake, so that we wish to evaluate measures such as extra probability of death per unit of action (per cigarette smoked, or per ton of coal mined, for example).

Death is not the only measure of risk of interest, for, although it is probably the most objective one and for this reason often used, it may not capture large components of what are perceived as risks. In balanced decisions it may become vital to consider other measures. A few possible such measures are:



This form of analysis constitutes an all-at-once technique, but one that is less useful than the preceding example (chemical hazards) because it gives no clue as to how to reduce the risks. The limitation can be overcome if it is possible to analyze each event leading to risks as a sequence of well-understood events forming an event tree. A set of event trees would cover all possible cases leading to the final risky event.

The most well-known use of event tree analysis is, perhaps, the analysis of nuclear reactor accidents in the so-called Rasmussen report (Nuclear Regulatory Commission 1975). The procedure will be briefly outlined here with a highly simplified example from the report. The first step is identification of all possible sequences of events that may lead to serious consequences to public health and safety, followed by the separation of these sequences into segments that are approximately independent of each other. By analyzing each event in each sequence separately, using theory or past experience or both, the overall probability of occurrence of the whole sequence can be evaluated. Thus the most probable (highly simplified) sequence for catastrophic failure in a PWR is shown in Figure 3-6. The overall accident probability (with assumptions to be mentioned) is then equal to

Probability of a pipe break (from theory and past data on other pipes)

- x probability of failure of emergency core cooling system (from a fault tree analysis)
- X probability of containment violation (more fault trees)
- X probability of unfavorable weather (past data on wind patterns, rainfall, and so on)
- $= p_1 p_2 p_3 p_4$.

The accident described by this event tree is initiated by the break of a water pipe in the cooling system causing loss of coolant and resulting, if the emergency core cooling system subsequently fails, in the meltdown of the reactor core and the release of the fission products therein. This may cause a violation of the concrete containment vessel, so that if the wind direction is right the released fission products may be blown over population centers, possibly causing radiation overdoses to a large segment of the population. In each case the probability of the event and also its severity must be evaluated. As indicated, the probability (p_1) of a pipe break may be estimated from historical experience with pipes first in other industries, sec-

cases are examined in detail major flaws and weaknesses can be discovered. We are heartened, however, by the realization that many of the flaws can easily be remedied and that in at least one case (saccharin) common sense filled in the gaps.

Before beginning a detailed discussion of individual studies, it is useful to picture an idealized scheme (Figure 6-1) of the complete decision process, and the place of risk assessment within it. Information is passed from scientist, engineer, and economist to risk assessor and to cost and benefit assessors. The results of these assessments and comparisons between them are made available to the decision-

Figure 6-1. Idealised Scheme for Risk Analysis.

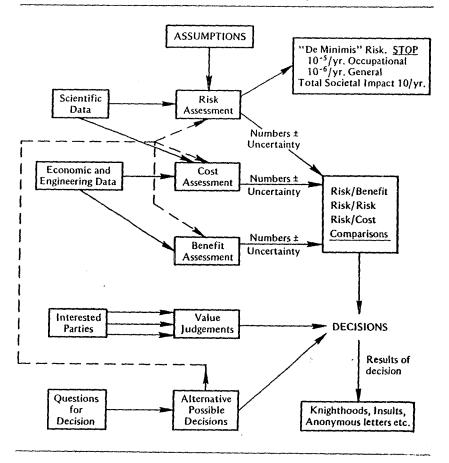


Table 7-1. Some One in a Million Risks.

Living in the United States: Time to accumulate a one in a million risk of death from the cause indicated.

| Motor vehicle accident | 1.5 | days |
|------------------------|-----|--------|
| Falls | 6 | days |
| Drowning | 10 | days |
| Fires | 13 | days |
| Firearms | 36 | days |
| Electrocution | 2 | months |
| Tornadoes | 20 | months |
| Floods | 20 | months |
| Lightning | 2 | years |
| Animal bite or sting | . 4 | years |

Occupational Risks. Time to accumulate a one in a million risk of death in the occupation indicated.

General

| | |
|--------------------------------|----------|
| Manufacturing | 4.5 days |
| Trade | 7 days |
| Service and Government | 3.5 days |
| Transport and Public Utilities | 1 day |
| Agriculture | 15 hours |
| Construction | 14 hours |
| Mining and Quarrying | 9 hours |
| | |

Specific

| Coal Mining (accidents) | 14 hours |
|-------------------------|----------|
| Police duty | 1.5 days |
| Railroad Employment | 1.5 days |
| Fire Fighting | 11 hours |

Other Risks.

Cosmic Rays.

One transcontinental round trip by air.

Living 1.5 months in Colorado compared to New York. Camping at 15,000 feet for 6 days compared to sea level.

Other Radiation

- 20 days of sea level natural background radiation.
- 2.5 months in masonry rather than wood building.
- 3/7 of a chest X-ray using modern equipment.

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Table 7-1. continued

Eating and Drinking.

40 diet sodas (saccharin)

6 pounds of peanut butter (aflatoxin).

180 pints of milk (aflatoxin).

200 gallons of drinking water from Miami or New Orleans.

90 pounds of broiled steak (cancer risk only).

Smoking

2 cigarettes

Source: Tables 7-2 to 7-5.

clearly into categories within which intercomparison is more easily justified and probably more accurate. Table 7-2 is a list of various commonplace risks of death, most of which would be considered involuntary. Notice that there may be some overlapping between categories (home accidents, for example, includes falls within the home). Table 7-3 shows some occupational risks, mostly risks of fatal accidents. Again, most such risks would be considered involuntary by those exposed. Table 7-4, in contrast, shows a set of voluntary risks of death, those incurred in sporting activities. Table 7-5 is a further set of everyday risks, but now specialized to cancer risks, selected because such risks arouse particularly strong emotions.

Before discussing these risks in more detail and indicating how they are all estimated, we would like to give another example that may help place these risks in perspective. Four tablespoons of peanut butter per day is shown as giving a risk of liver cancer of 8×10^{-6} per year, or a lifetime risk of 6×10^{-4} . But four tablespoons of peanut butter corresponds to 400 kilocalories (Kcal), so if one were to eat only peanut butter, daily energy requirements would be supplied by 26 tablespoons per day, giving a lifetime liver cancer risk of 4×10^{-3} , or 0.004. This should be compared with a lifetime probability of any kind of cancer of about 0.25, even in the absence of peanut butter.

Table 7-2. Some Commonplace Risks of Death in the United States, Based on Estimated U.S. Resident Population (Source 1).

| Risk | Annual per Capita Risk ^a | Annual Trend ^b | Variability, Percent ^c | Based On | Source |
|-------------------------------------|--|------------------------------|--------------------------------------|------------|---------------|
| Motor vehicle accident | | | | | - |
| Total | 2.4×10^{-4} | • • • | 10 | 1950-78 | 1 |
| Collision with pedestrian | 4.2×10^{-5} | -3.9×10^{-7} | 10 | 1950-78 | 2 |
| Home accidents ^d | 1.1×10^{-4} | -2.9×10^{-6} | 5 | 1950-78 | 2 |
| Falls | 6.2×10^{-5} | -3.0×10^{-6} | 6 | 1963-77 | 2 |
| Drowning | 3.6×10^{-5} | | 7 | 1963-77 | 2 |
| Fires | 2.8×10^{-5} | -1.0×10^{-6} | 5 | 1963-77 | 2 |
| Inhalation and ingestion of objects | 1.5×10^{-5} | | 10 | 1968-77 | 2 |
| Firearms | 1.0×10^{-5} | -2.4×10^{-7} | 8 | 1968-77 | 2 |
| Accidental poisoning | | | | | |
| Gases and vapors | 7.7×10^{-6} | • • • | 5 | 1963-77 | 2 |
| Solids and liquids | | | | 3 | |
| (Not drugs or medicaments) | 6.0×10^{-6} | ••• | 10 | 1971-77 | 2 |
| Electrocution | 5.3×10^{-6} | • • • | 5 | 1971-77 | 2 |
| Tornadoes | 6×10^{-7} | • • • | 100 | 1950-77 | 1 |
| Floods | 6×10^{-7} | | 100 | 1950-77 | 1 |
| Lightning | 5×10^{-7} | | 18 | 1971-77 | 2 |
| Tropical cyclones and hurricanes | 3×10^{-7} | • • • | 160 | 1952-77 | 1 |
| Bites and stings by venomous | 9 | | | | |
| animals and insects | 2.4×10^{-7} | • • •, | 13 | 1971-77 | 2 |
| Air Pollution | 2.4×10^{-4} | | | -see text- | |

a. Average over indicated years, if no trend is shown. The value of trend line in last year of indicated years is used if a trend is shown.

b. Average annual change of annual per capita risk during years shown. Least squares straight line fit of annual risk versus time. A trend is shown if the estimated trend was significant at the 5 percent level (two-tailed).

c. Estimated standard deviation of annual per capita risk about the trend line (trend) or of the mean value (no trend).

d. Home accidents includes some proportion of some of the following seven risks.

Sources: 1. U.S. Bureau of the Census (1975, Annual). 2. National Safety Council (Annual).

| Occupation or Industry | Annual Risk ^a | Annual Trend ^b | Variability, Percent ^c | Based On | Source |
|--|--------------------------|------------------------------|--------------------------------------|----------|--------|
| Manufacturing | 8.2 × 10 ⁻⁵ | -1.6×10^{-6} | 8 | 1955-78 | 1 |
| Trade | 5.3×10^{-5} | -2.3×10^{-6} | 15 | 1955-78 | 1 |
| Service and government | 1.0×10^{-4} | -2.0×10^{-6} | 8 | 1955-78 | 1 |
| Transport and public utilities | 3.7×10^{-4} | | 16 | 1955-78 | 1 |
| Agriculture ^d | 6.0×10^{-4} | ••• | 9 | 1955-78 | 1 |
| Construction | 6.1×10^{-4} | -7.0×10^{-6} | 6 | 1955-78 | 1 |
| Mining and Quarrying | 9.5×10^{-4} | • • • | 22 | 1955-78 | 1 |
| Farming ^e | 3.6×10^{-4} | -5.0×10^{-6} | 7 | 1964-77 | 1, 2 |
| Tractor fatalities per tractor | 8.8×10^{-5} | -1.0×10^{-5} | 22 | 1969-77 | 1 |
| Metal mining and milling | 9.4×10^{-4} | ' | 15 | 1959-71 | 3 |
| Nonmetal mining and milling | 7.1×10^{-4} | $+2.3 \times 10^{-5}$ | 15 | 1959-71 | 3 |
| Stone quarries and mills | 5.9×10^{-4} | | 20 | 1959-71 | 3 |
| Coal mining (accidents) | 6.3×10^{-4} | -1.0×10^{-4} | 46 ^f | 1963-77 | 4 |
| Police officers killed in line of duty | | | | | |
| Total | 2.2×10^{-4} | | 19 | 1975-78 | 4 |
| By felons | 1.3×10^{-4} | -2.1×10^{-5} | 8 | 1975-78 | 4 |
| Railroad employees | 2.4×10^{-4} | -6.0×10^{-6} | 7 | 1963-77 | 1, 4 |
| Steel worker (accident only) | 2.8×10^{-4} | • • • | ? | 1969-72 | 5 |
| Fire fighter | 8.0×10^{-4} | | ? | 1971-72 | 5 |

EVERYDAY LIFE: A CATALOGUE OF RISKS

a. Per person at risk. Average over indicated years, if no trend is shown. The value of trend line in last year of indicated years is used if a trend is shown.

b. Average annual change of annual risk during indicated years. Least squares straight line fit of annual risk versus time. A trend is shown if the estimated trend was significant at the 5 percent level. Note that the error estimates for these trends are generally large.

c. Estimated standard deviation of annual risk about the trend line (trend) or of the mean value (no trend). Expressed as a percentage of the risk shown in the first column.

d. Not strictly comparable with farming category, includes transport accidents and all agriculture.

e. Not strictly comparable with agriculture category, refers to nontransport deaths occurring on farms, the population at risk being assumed to be all employed workers, unpaid family members working more than fifteen hours per week and operators working more than one hour per week.

f. The large variability is due to the bad choice of model (straight line fit) and the large changes occurring in the years indicated.

Sources: 1. National Safety Council (Annual). 2. U.S. Department of Agriculture (1979). 3. U.S. Bureau of Mines (Annual). 4. U.S. Bureau of the Census (Annual). 5. Baldewicz et al. (1974).

2, 3

| Sport | Average Annual Risk ^b | Average Annual Deaths | Estimated Population at Risk | Years of Coverage | Source |
|------------------------------------|---|--------------------------|------------------------------------|----------------------|--------|
| Aerial acrobatics (professional) | $\lesssim 2 \times 10^{-3 \text{ d,h}}$ | 0.22 | 360 | 1970-78 | 1 |
| Air show/air racing and acrobatics | 5×10^{-3} | 4.9 | 1,050° | 1971-77 | 1 |
| Flying amateur/home built aircraft | 3×10^{-3} | 25 | 8,000° | 1970-77 | 1 |
| Bicycle racing (registered) | $\lesssim 9 \times 10^{-5}$ d,e | 0.33 | 9,800 | 1970-78 | 1 |
| Boating | 5×10^{-5} | 1,300 | 27×10^{6} | 1972-78 ^j | 2, 3 |
| Bobsledding | $\lesssim 7 \times 10^{-4} d, f$ | 0 | 450 | 1970-78 | 1 |
| Football | | • | | | |
| Sandlot | 2×10^{-6} | 1.7 | 10 ⁶ | 1970-78 | 1 |
| Professional and Semiprofessional | $\lesssim 4 \times 10^{-4}$ d,g | 0.11 | 1,500 | 1970-78 | 1 |
| High school | $\sim 1 \times 10^{-51}$ | 13 | 10 ⁶ | 1970-78 | 1 |
| College | 3×10^{-51} | 1.2 | 40,000 | 1970-78 | 1 |
| Glider flying | 4×10^{-4} | 7 | 18,000° | 1970-77 | 1 |
| Hang gliding | $\sim 8 \times 10^{-4}$ | 31 | 20,000-60,000 | 1974-78 | 1 |
| Hunting | 3×10^{-5} | 600-800 | 22×10^{6} | 1972 | 2, 3 |
| Ice yachting | $\lesssim 1 \times 10^{-4 d, h}$ | 0.22 | 4,500-6,500 | 1970-78 | 1 |
| Lighter-than-air flying | 9 x 10 ⁻⁴ | 2.6 | 3,000° | 1970-77 | 1 |
| Mountaineering | 6×10^{-4} | 34 | 60,000 | 1970-78 | 1 |
| Mountaineering k | 7×10^{-4} | 12 | 19,000 | 1951-60 | 4 |
| Power boat racing | 8 x 10 ⁻⁴ | 5.2 | 6,500 | 1970-78 | 1 |
| Professional stunting | $\lesssim 1 \times 10^{-2} d, i$ | 1 | 200 | 1975-78 | 1 |
| Rodeo | $\lesssim 3 \times 10^{-5} \mathrm{d,e}$ | 0.33 | 34,000 | 1970-78 | 1 |
| | | | | | |
| Scuba diving | 4 × 10 ⁻⁴ | 126 | 300,000 | 1970-76 | 1 |
| Ski racing | 2×10^{-5} | 2 | 81,000 | 1970-78 | 1 |
| Spelunking | $\lesssim 1 \times 10^{-4} \mathrm{d}$, i | 0.44 | 10,000 | 1970-78 | 1 |
| Sport parachuting | $\sim 2 \times 10^{-3}$ | 41 | 25,000 | 1970-78 | 1 |

a. No error estimates are given. The reason is that, although we could give statistical sampling errors on the risks shown, the population size is so uncertain in most cases (by a factor of 2 to 3) that this uncertainty dominates.

2.6

2,600

1,800

 82×10^{6}

1970-78

1972-78^j

 1×10^{-3}

 3×10^{-5}

Thoroughbred horseracing

Swimming

b. Per person at risk. See preceding note on error estimates.

c. This population corresponds only to pilots certified by the Federal Aviation Administration.

d. The value shown is statistical 95 percent confidence upper bound, assuming risk proportional to person-years of exposure and a Poisson distribution of deaths. See also note a on error estimates.

e. Three deaths observed in time indicated.

f. No deaths observed in time indicated.

g. One death observed in time indicated.

h. Two deaths observed in time indicated.

i. Four deaths observed in time indicated.

j. Population figures from 1972, deaths from 1978. We have assumed a similar population went swimming or boating in 1978.

k. Not strictly comparable with the preceding entry, also labeled Mountaineering. The figure in the population column is total man-mountainays, and the risk is per man-mountain-day. This agrees with the previous figure for annual risk if an average of ~ 0.9 days per year is spent mountaineering, but note that the years of coverage differ also.

^{1.} If participation has remained constant, as we assume, there are possibly decreasing trends in these risks.

Sources: 1. Metropolitan Life Insurance Company (1979). 2. U.S. Bureau of the Census (Annual). 3. National Safety Council (Annual). 4. Fers (1963). (The article also discusses some of the problems of interpretation of risks such as those shown in this table).

| | Annual Average Risk ^c | Estimated Uncertainty d | Source |
|--|---|-----------------------------|---|
| Current Cancer Raïes ^b | | | |
| All Cancers Buccal cavity, pharynx, respiratory Digestive organs and peritoneum Bone, connective tissue, skin, breast Genital organs Urinary tract Other Leukemia and other blood and lymph | $ \begin{array}{c} 2.8 \times 10^{-3} \\ 7.2 \times 10^{-4} \\ 7.5 \times 10^{-4} \\ 3.1 \times 10^{-4} \\ 3.2 \times 10^{-4} \\ 1.2 \times 10^{-4} \\ 2.7 \times 10^{-4} \\ 2.6 \times 10^{-4} \end{array} $ | ~ 20% | 1 |
| Cosmic Ray Risks ^f | | | |
| Airline pilot (50 hours per month at 12 kilometers altitude) One transcontinental round trip by air per year Frequent airline passenger (4 hours per week flying) Living in Colorado compared to New York Camping at 15,000 feet for 4 months per year | $ \begin{array}{c} 4 \times 10^{-5} \\ 10^{-6} \\ 10^{-5} \\ 8 \times 10^{-6} \\ 2 \times 10^{-5} \end{array} $ | Factor of 3 ^f | $ \left(\begin{array}{c} 2\\2\\2\\3\\3\\3\end{array}\right) $ |
| Other Radiation Risks | | | } |
| Natural background radiation (sea level) Average diagnostic medical X-rays in the United States Living in masonry building rather than wood | $\begin{array}{c} 2.0 \times 10^{-5} \\ 2.0 \times 10^{-5} \\ 5.0 \times 10^{-6} \end{array}$ | | 3 4 5 |
| Eating and Drinking | | | |
| One 12½ ounce diet drink per day Average saccharin consumption in the United States Four tablespoons peanut butter per day ¹ One pint milk per day ¹ Miami or New Orleans drinking water ½ lb. charcoal broiled steak per week | $ \begin{array}{c} 10^{-5} \\ 2.0 \times 10^{-6} \\ 8.0 \times 10^{-6} \\ 2.0 \times 10^{-6} \\ 10^{-6} \end{array} $ | Factor of order 10 | See text. |
| (cancer risk only; heart attack and other risks additional) | 3.0×10^{-7} | | |
| Alcohol, averaged over smokers and nonsmokers ⁸ Alcohol, light drinker (one beer per day) ⁸ | $ \begin{array}{c} 5.0 \times 10^{-5} \\ 2.0 \times 10^{-5} \end{array} $ | Factor of order 10 | See text. |
| Tobacco ^h | | | |
| Smoker, cancer only Smoker, all effects (including heart disease) | $ \begin{array}{c} 1.2 \times 10^{-3} \\ 3.0 \times 10^{-3} \end{array} $ | Factor of 3 | See text. |
| Person sharing room with smoker | 10 ⁻⁵ | Factor of 10 | |
| Air Pollution | | | |
| Polycyclic organics, all effects | 1.5 × 10 ⁻⁵ | See text. | See text. |

a. These are risks of death, the difference between incidence and mortality being well within the uncertainties shown, (except for the Current Cancer Rates category.

- c. Averaged over the whole population of the United States.
- d. Even the uncertainties in these estimates can be very large. The uncertainties are mostly estimated subjectively and are conditional on the models used for extrapolation being approximately correct.
 - e. Averaged over males and females. The risk is approximately double for females only.
- f. We assume a linear model with a total of 1 cancer per 5,000 man-rem, corresponding to BEIR 1972. More recent estimates of the BEIR committee (1980) would give slightly lower estimates.
- g. Cirrhosis of the liver. Not a cancer, but included here since the methods used are similar. It is possible that in this case there is a threshold effect for damage. In addition there is some evidence that moderate alcohol consumption is associated with lower death rates from other diseases.
 - h. Based on human data.
 - Based on human data for aflatoxin carcinogenicity. Note that we assume that the measured aflatoxins are aflatoxin B, the most potent. If a corresponds to other aflatoxins, these estimated risks should be reduced.

Sources: (The following references are the sources of data used in the models. We have estimated the risks). 1. U.S. Department of Health, Education and Welfare (1975). 2. United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR) (1962). 3. Oakley (1972). 4. United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR) (1977). We have used the bone marrow dose here. 5. Moeller and Underhill (1976).

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b. Included to give some perspective. The figures given correspond approximately to the lifetime risk divided by the lifetime. The lifetime risk is estimated by the fraction of those dying who die of the given cancer, average lifetime is estimated as seventy years. Since cancer rates increase rapidly with age and the population age structure is changing, these figures are only approximate. Data from Vital Statistics of the United States, 1975.

Risk Management Commentary
for
Dr. D. Allan Bromley
Assistant to the President
for
Science and Technology

I. Presidential Objectives:

- 1. The very best science should determine the allocation of resources. Public fears drive much of regulatory and Congressional actions. These public concerns are often inconsistent with science-based selection of those factors most effective in improving public health.
- 2. Coherent policies, methodologies, and procedures for establishing regulatory objectives of the federal agencies on a scientific basis. These should effectively incorporate current science, peer review, and public participation.
- 3. Maximize the effectiveness of our huge national expenditures arising from regulations for improving health and safety by a balanced allocation of priorities and resources.
- 4. Minimize congressional prescriptions on details of risk management to give the agencies more flexibility to meet regulatory objectives with minimal impact on economic activities.

II. Recommendations:

- 1. Appoint a deputy for a full-time focus on Risk Assessment and Management. Select someone who understands the complexities of the issues.
- 2. Establish a Council (or PCAST Subcommittee) on Risk Assessment and Management for review and guidance of agency criteria, methodologies and procedures. This would provide scientific oversight on proposed agency activities and regulations. It would also coordinate the large number of existing government committees and programs already engaged on specific agency tasks.
- 3. Coordinate with OMB on the process for economic evaluations and agency implementation of OMB procedural recommendations.

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4. Initiate a public education program on the realities of risks and choices (both governmental and individual), comparative risks, benefit-risk balance, and the acceptability of low-level exposures in daily life. The Society for Risk Analysis may be a vehicle for such a program. Modest financial support would be needed for workshops, bulletins, teaching material, etc.

III. Background Issues:

The cumulative national direct cost burden of proposed reductions of environmental risks is likely to exceed \$100 billions per year (e.g. clean air, toxic, CFCs, CO2, electricity fields, house radon, hazardous waste, etc.). Indirect costs will increase this burden. These costs will become publicly apparent through their large inflationary effect on costs. They cannot be ignored. Unfortunately, there is no upper bound to such expenditures as long as "zero" risk is the political target, except a national resource limitation. Recognizing that poverty is the greatest social pollutant, the effect on the productivity of the economy must be considered.

Congress has implied in several acts that the cost of meeting health and safety objectives should not be considered in setting regulatory objectives. However, this does not preclude the establishment of regulatory targets consistent with the optimal distribution of our resources to improve health and safety. This is a central issue, as it is the operational intersection of risk assessment with risk management. Even a crude disclosure of the relative importance of risks might diminish the prescriptive tendencies of Congress, and shift the decision initiatives to the agencies on the allocation of funds and attention.

Public confidence in the wisdom, objectivity, credibility, and feasibility of government regulatory actions is an essential objective. This requires that the suggested OSTP Council be broadly based with expertise from all stakeholders (academia, government, industry, public groups, etc.) and is constituted to consider risk assessment, management, and communication. Obviously, such a Council would need staff support for organizing briefings, discussions, and fundings.

IV. Risk Assessment:

The quantitative establishment of the relationship between public exposure to a hazard and its health and safety consequences suffers from several handicaps.

- 1. Analytic uncertainties become larger as the exposure levels per person becomes smaller because the data base becomes vague and finally nonexistent. At the same time, the number of people involved tends to increase, so the cumulative public risk becomes indeterminate. As a substitute for scientific information, agencies use simplified extrapolations of high level data and "worst case" projections for regulatory purposes.
- 2. The agencies treat each hazard as an independent source of risk, and use fixed criteria for setting targets (e.g. EPA's 1 in a million lifetime risk). Comparative risk analysis is generally absent, although implicit balancing of the public perceptions of the relative importance of risks is subconsciously involved in agency attention.
- 3. The "worst case" syndrome pervades agency decisions. Given the uncertainties of the data, it is easier to publicly defend a "worst case" choice. However, the economic consequences may be extremely large, particularly when orders of magnitude are involved.
- 4. It is impossible to consistently use "worst case" analysis. Agencies tend to apply "worst case" projections to selected situations they choose to analyze, and to ignore the actual risks of unanalyzed hazards. This tends to make regulation arbitrary, capricious, and independent of the actual risk.

V. Risk Management:

- 1. There are no generally accepted measures as yet developed to compare the unlike consequences of a variety of risks (e.g. life threatening vs physical impairment, human vs ecologic, physical vs psychological, short term vs long term, etc). Nevertheless, such implicit evaluations are being made, and are shaped by the cultural biases of the decision makers.
- 2. There are no guidelines for comparative cost-effectiveness of the remedial measures imposed by regulations to achieve improvement in health or ecology, or of the reduction of involuntary exposures to risks. Regulations

are usually justified on the basis of individual risk reductions, without reference to the comparative cost-effectiveness of other risk reduction measures.

- 3. The responsibility for the implementation of risk management is shared in practice between government, industry, and the public. This is a very complicated interaction and can only be successful if all sectors agree on the objectives. In this respect, the Nuclear Regulatory Commission has pioneered in a sharing of responsibilities with the industry. It should be studied as a developing risk management system.
- 4. The individual exposure to risks arises from food, water, air, industry, lifestyle systems, work, etc. Many federal agencies are involved (FDA, EPA, NRC, HHS, OSHA, DOE, DOD, DOT, etc.). The need for an Executive Office guidance and overview has been growing during this past decade.
- 5. The financial consequences of risk management regulations may be one of our largest national cost factors, indirectly comparable to health services and defense. It requires a scientific basis for rational decision making. It deserves OSTP attention at the highest level.
- 6. The Senate version of the Clean Air Act, S.1630, contains a long section on the establishment of a 10 member Risk Assessment and Management Commission. As presently proposed, this Commission reports to the President and Congress. It is intended to have a 4 year life. If this legislation is passed, its relationship to PCAST and the OSTP should be considered. This proposed Commission is focussed on air pollution., The OSTP interest should encompass the wider spectrum of risks covered by other federal agencies.

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Articles

Risk Assessment and Comparisons: An Introduction

RICHARD WILSON AND E. A. C. CROUCH

Risk assessment is presented as a way of examining risks so that they may be better avoided, reduced, or otherwise managed. Risk implies uncertainty, so that risk assessment is largely concerned with uncertainty and hence with a concept of probability that is hard to grasp. The results of even the simplest risk assessments need to be compared with similar assessments of commonplace situations to give them some meaning. We compare and contrast some risk estimates to display their similarities and differences.

VERY DAY WE TAKE RISKS AND AVOID OTHERS. IT STARTS AS soon as we wake up. One of us lives in an old house that had old wiring. Each time he turned on the light, there was a small risk of electrocution. Every year about 200 people are electrocuted in the United States in accidents involving home wiring or appliances, representing a risk of death of about 10^{-6} per year, or 7×10^{-5} per lifetime. To reduce this risk, he got the wiring replaced. When we walk downstairs, we recall that 7000 people die each year in falls in U.S. homes. But most are over 65, so we pay little attention to this risk since both of us are younger than that.

How should we go to work? Walking is probably safer than using a bicycle, but would take five times as long and provide less healthful exercise. A car or, better, public transport would be both safer and faster. Expediency wins out, and the car comes out of the garage. Fortunately, the choice nowadays is not between horse or canoe—both of which are much more dangerous. The day has just begun, and already we are aware of several risks, and have made decisions about them.

Most of us act semi-automatically to minimize our risks. We also expect society to minimize the risks suffered by its members, subject to overriding moral, economic, or other constraints. In some cases these constraints will dominate, in others there will be trade-offs between the values assigned to risks and the constraints. Risk assessments, except in the simplest of circumstances, are not designed for making judgments, but to illuminate them (I). To effectively illuminate, and then to minimize, risks requires knowing what they are and how big they are. This knowledge usually is gained through experience, and the essence of risk assessment is the application of this knowledge of past mistakes (and deliberate actions) in an attempt to prevent new mistakes in new situations.

The results of risk assessments will necessarily be in the form of an estimate of probabilities for various events, usually injurious. The goal in performing a risk assessment is to obtain such estimates, although we consider the major value in performing a risk assess-

autough we consider the major value in performing a risk assess-

ment is the exercise itself, in which (ideally) all aspects of some action are explored. The results, goals, and values of performing the risk assessment must be sharply contrasted with the cultural values assigned to the results. Such cultural values will presumably be factors influencing societal decisions and may differ even for risk estimates that are identical in probability.

Risk and Uncertainty

The concept of risk and the notion of uncertainty are closely related. We may say that the lifetime risk of cancer is 25%, meaning that approximately 25% of all people develop cancer in their lifetimes. Once an individual develops cancer, we can no longer talk about the risk of cancer, for it is a certainty. Similarly if a man lies dying after a car accident, the risk of his dying of cancer drops to near zero. Thus estimates of risks, insofar as they are expressions of uncertainty, will change as knowledge improves.

Different uncertainties appear in risk estimation in different ways (2). There is clearly a risk that an individual will be killed by a car if that person walks blindfolded across a crowded street. One part of this risk is stochastic; it depends on whether the individual steps off the curb at the precise moment that a car arrives. Another part of the risk might be systematic; it will depend on the nature of the fenders and other features of the car. Similarly, if two people are both heavy cigarette smokers, one may die of cancer and the other not; we cannot tell in advance. However there is a systematic difference in this respect between being, for instance, a heavy smoker and a gluttonous eater of peanut butter, which contains aflatoxin. Although aflatoxin is known to cause cancer (quite likely even in humans), the risk of cancer from eating peanut butter is much lower than that from smoking cigarettes. Exactly how much lower is uncertain, but it is possible to make estimates of how much lower and also to make estimates of how uncertain we are about the

Some estimates of uncertainties are subjective, with differences of opinion arising because there is a disagreement among those assessing the risks. Suppose one wishes to assess the risk (to humans) of some new chemical being introduced into the environment, or of a new technology. Without any further information, all we can say about any measure of the risk is that it lies between zero and unity. Extreme opinions might be voiced; one person might say that we should initially assume a risk of unity, because we do not know that the chemical or technology is safe; another might take the opposite extreme, and argue that we should initially assume that there is zero risk, because nothing has been proven dangerous. Here and elsewhere, we argue that it is the task of the risk assessor to use whatever information is available to obtain a number between zero and one for a risk estimate, with as much precision as possible, together with an estimate of the imprecision. In this context, the statement "I do not know" can be viewed only as procrastination

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and not responsive to the request for a risk estimate (although this should not be read as condemning procrastination in all circumstances).

The second extreme mentioned, the assumption of zero risk, can arise because people and government agencies have a propensity to ignore anything that is not a proven hazard. We argue that this attitude is inconsistent if the objective is to improve the public health, may also lead to economic inefficiencies, and often leads to unnecessary contention between experts who disagree strongly. Fortunately, if risk assessors have been diligent in searching out hazards to assess, few hazards posing large risks will be missed in this way, so that there may be minor direct danger to human health from a continuation of the attitude.

Risk Estimation Based on Historical Data

The way in which risks are perceived is strongly correlated with the way in which they are calculated. Risks based on historical data are particularly easy to understand and are often perceived reliably. It is therefore easy to illustrate a risk calculated from historical data to understand some characteristics of risk estimation. There are plenty of data on automobile accidents (although never enough to make risk assessors happy). One thing that these data can tell us is the frequency of such accidents in the past and their trend through time. To make predictions, however, we must use a model. The simplest model is that there will be as many accidents next year as last, to within a statistical error of the square root of the number. A slightly more complicated, but perhaps more accurate, model might be to fit a mathematical function to numbers from previous years and to argue that next year's accidents will follow the trend given by this function. A possibly better and possibly more accurate model still might use all available information that might influence accident trends. For example, an oil embargo with a concomitant rise in oil price and reduction in automobile travel would be likely to reduce the risk of accident. In any event, it becomes clear that it is impossible to calculate any risk without a model of some sort, even the simple one that tomorrow will be like today.

Risks of New Technologies

We can only use the historical approach to estimating risks when the hazard (for example, technology, chemical, or simply some action) has been present for some time and the risk is large enough to be directly measured (although when it is not large enough to be

Table 1. Comparison of several common radiation risks.

| Action | Dose (mrem/ year) | Cancers if all U.S. population exposed (assuming linearity) |
|---|-------------------------|--|
| Medical x-rays | 40 | 1100 |
| Radon gas (1.5 pCi/liter, equivalent dose)* | 500 | 13,500 |
| Potassium in own body | 30 | 1000 |
| Cosmic radiation at sea level | 40 | 1100 |
| Cosmic radiation at Denver | 65 | 1800 |
| Dose to average resident near Chernobyl first year | 5000 | Not relevant |
| One transcontinental round trip by air | 5 | 135 |
| Average within 20 miles of nuclear plant | 0.02 | · >1 |

^{*}The radon exposure is to the lungs and cannot be directly compared to whole body external exposure. The comparison here is on the basis of the same magnitude of risk. The uncertainty of the radon number is at least a factor of 3.

Table 2. Some commonplace risks (mean values with uncertainty).

| Action | Annual risk | Uncertainty |
|---|---|-------------------------------|
| Motor vehicle accident (total) Motor vehicle accident (pedestrian only) | $\begin{array}{c} 2.4 \times 10^{-4} \\ 4.2 \times 10^{-5} \end{array}$ | 10% 10% |
| Home accidents Electrocution | 1.1×10^{-4} 5.3×10^{-6} | 5% 5% |
| Air pollution, eastern United States | 2×10^{-4} | Factor of 20 downward only |
| Cigarette smoking, one pack per day | 3.6×10^{-3} | Factor of 3 |
| Sea-level background radiation (except radon) | 2×10^{-5} | Factor of 3 |
| All cancers | 2.8×10^{-3} | 10% |
| Four tablespoons peanut butter per day | 8×10^{-6} | Factor of 3 |
| Drinking water with EPA limit of chloroform | 6×10^{-7} | Factor of 10 |
| Drinking water with EPA limit of trichloroethylene | 2×10^{-9} | Factor of 10 |
| Alcohol, light drinker | 2×10^{-5} | Factor of 10 |
| Police killed in line of duty (total) | 2.2×10^{-4} | 20% |
| Police killed in line of duty (by felons) | 1.3×10^{-4} | 10% |
| Frequent flying professor | 5×10^{-5} | 50% |
| Mountaineering (mountaineers) | 6×10^{-4} | 50% |

measured, an upper limit may be calculated, if one assumes some sort of model). If there is no historical database for the hazard (a new power plant or industrial facility, for instance), one approach is to consider it in separate parts, calculating the risks from each part and adding them together to estimate a risk for the whole. For example, all possible chains of events from an initiator to a final accident are followed in an "event tree," with the probabilities of each event in the tree being estimated from historical data in different situations.

A particularly well-known example is the calculation of the probability of a severe accident at a nuclear power plant (3). That this procedure has at least a partial validity is due to the fact that the design of nuclear power plants proceeded in approximately this factorable way; attempts were made to imagine all major accident possibilities, "maximum credible accidents" or "design basis accidents," and then to add an independent device to prevent this accident from having severe consequences. To the extent that the added safety device is independent, the failure probability is independent, and the small overall accident probability is the product of individual failure probabilities which are larger.

Risks by Analogy: Carcinogenic Risks

Some carcinogenic risks may be estimated from historical data. But this is complicated by the time delay between the insult and the final cancer, one reason why causality is hard to prove if the risk is small. This is the difficult field of epidemiology.

Although some of the largest cancer risks have been identified through the use of epidemiology (4), preventive public health suggests that we endeavor to estimate risks even where no historical data exist and the risk is small. This is often done by analogy with the cancer risks to animals, usually rodents, which are deliberately exposed to large enough quantities of pollutant so that an effect is observed. To use these data to estimate the risk at low doses in people involves (to oversimplify matters) two difficult steps: the comparison of carcinogenic potency in animal and man (5-7) and the extrapolation from a high dose to a low dose. Because both steps require a certain amount of theory, they are controversial. Indeed, there are those who regard the uncertainty as so great that they prefer not to provide numerical estimates of risk (8, 9), although they may order materials in carcinogenic potency. The difference

between this and providing a numerical estimate is important, but is one of presentation rather than substance.

If there are no animal data, or if in an animal experiment there is no statistically significant effect, it does not necessarily mean that there is no risk. If the experimenters have been diligent, the risk is probably small, although never zero, even though that may be the best estimate. Various attempts are made to use data even less direct than the animal bioassays to estimate risks in such cases. These include simple analogies based on chemical similarity (10), and comparison with outcomes other than cancer—for example, mutagenesis (11) and acute toxicity (12, 13). Not surprisingly, these more indirect procedures arouse even more controversy than the animal bioassays.

There have been few attempts to perform risk assessments for biological end points other than cancer. However, it is known that the pollutants in cigarette smoke cause at least as many deaths through heart problems as by cancer (14), and we should not be surprised if other carcinogens were to produce chronic effects other than cancer. For now, the cancer risk assessment has to act as surrogate for these other risks also.

Risk Value Versus Certainty of Information

After risks of a number of situations have been assessed, we often want to order them in order to decide which should command our attention. It is not always the order of increasing risk that is used for such purposes. There have been proposals to order potential carcinogens on other factors (8, 15), such as the certainty of information.

Vinyl chloride gas has been found to cause angiosarcomas both in people and in rats. Since an angiosarcoma is a rare tumor, the risk ratio (the ratio of the observed number of cancers in those exposed to the number expected by chance) is of order 100 or more in some cases. If an angiosarcoma is seen in a vinyl chloride worker, the attribution to vinyl chloride exposure is almost certain. On the other hand, the number of persons who have been heavily exposed to vinyl chloride is small, so that only about 125 angiosarcomas have been seen among vinyl chloride workers worldwide in the last 20 years. Now that exposures in the workplace have been greatly reduced, no angiosarcomas attributable to recent occupational exposure have been seen. We do not know the dose-response relation, but it is generally believed that the response falls at least linearly as the exposure is reduced, so that no more than one cancer is expected in several years.

We can compare this with the possible cancer incidence that was predicted by the Food and Drug Administration (FDA) in 1977 from use of saccharin (16). This was based on experiments with rats, leading to an additional uncertainty. More people ate saccharin than were exposed to vinyl chloride, and nearly 500 cancers per year were estimated for the United States alone. For vinyl chloride we therefore have the situation that the individual risk is now low, yet there is considerable certainty that there is a risk. For saccharin the risk is higher, but there is more uncertainty about the value of the risk. Some persons, in some situations, may demand that more attention be given to the risk from vinyl chloride than to the risk from saccharin; for other persons or situations the reverse may be the case.

Comparison of Risks

The purpose of risk assessment is to be useful in making decisions about the hazards causing risks, and so it is important to gain some

perspective about the meaning of the magnitude of the risk. Comparisons can be useful. We are not born with an instinctive féeling for what a risk of one in a million per lifetime means, although we do learn that some risks are small and others large. It is particularly helpful to compare risks that are calculated in a similar way. For example, the risk of traveling by automobile can be compared to that of traveling by horse with the use of historical data.

Another common procedure is to compare exposures only. Table 1 shows a list of radiation exposures in typical situations (17). The dose-response relation for radiations with similar energy deposition per unit track length will be similar, although there may be some correction required for dose-rate effects, so that ordering by exposure should be similar to ordering by risk. In estimating the number of lethal cancers on a linear hypothesis, we have here assumed approximately 8000 man-rems per cancer (at low doses), in itself uncertain by 30% or more.

An example of comparison of risks that are similarly calculated is the comparison of risks of various chlorinated hydrocarbons in drinking water. The risks to humans are estimated from carcinogen bioassays in rodents (rats and mice). Since these are similar materials, we might expect that the dose-response relationships have the same shape. Chloroform, which is produced by interaction of chlorine with organic matter during the chlorination of surface waters to kill bacteria, produces cancer in animals 20 times as readily as does trichloroethylene, an industrial solvent that is occasionally found in well waters as a result of accidental pollution. Although neither is known to cause cancer in people, we might expect that chloroform would do so about 20 times as readily.

Table 2 shows a variety of risks calculated in various ways and our estimate of the uncertainty. They are deliberately jumbled to provoke thought by juxtaposition. [Risk estimates quoted by the Environmental Protection Agency (EPA) for carcinogens tend to be greater than those shown in Table 2 by a factor approximately equal to the uncertainty factor—this is not accidental (5, 18).]

Contrasting Risks

Objections have been raised to risk comparisons on the ground that they are misleading. This would be true if all risks of the same numerical magnitude were treated in the same way. But they are not. In some cases it is useful to contrast risks to indicate the different ways in which they are treated in society. In Table 3 we give an example by comparing and contrasting the carcinogenic effects of aflatoxin B1 and dioxin, both among the most carcinogenic chemicals known. The difference in treatment of these two materials is perhaps a reflection of different values assigned to various aspects of the problems caused by their presence.

Aflatoxin and dioxin have similar toxicities and carcinogenic potency (perhaps within a factor of 10, although both measures for both chemicals vary substantially with species tested). The certainty of information for aflatoxin is great. There is less information about carcinogenicity of dioxin. Dioxin may be a promoter and pose a minuscule risk at low doses, whereas aflatoxin is almost certainly an initiator also. Nonetheless such standards as there are appear to be more stringent for dioxin, possibly because dioxin is an artificial chemical and possibly because it was a trace component of a chemical mixture (Agent Orange) that was used in warfare.

The small risk of a large accident in a nuclear power plant can also be contrasted with the more numerous small accidents or events that occur every day in the mining, transport, and burning of coal. One feature that is brought out clearly here is that we do not always compare the risk averaged over time, but worry more about risks that are sharply peaked in time.

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Expression of Risks

Just as a comparison of risks is an aid in understanding them, so is a careful selection of the methods of expression. It is hard to comprehend the statistical (stochastic) nature of risk. There are ways to mitigate this difficulty in comprehension. We are almost all used to one such statistical concept—the expectation of life. When we talk about the expectation of life being 79 years (for a nonsmoking male in the United States) we all know that some die young and that many live to be over 80. Thus the expression of a risk as the reduction of life expectancy caused by the risky action conveys some of the statistical concept essential to its understanding. One particular calculation of this type can be used as an anchor for many people, because it is easy to remember. The reduction of life expectancy by smoking cigarettes can be calculated from the risk, one in 2 million, of smoking one cigarette, multiplied by the difference of the average life-span of a nonsmoker and a lung cancer victim. This turns out to be 5 minutes, or the time it takes to smoke the one cigarette.

It is important to realize that risks appear to be very different when expressed in different ways (19). One example of this can be seen if we consider the cancer risk to those persons exposed to radionuclides after the Chernobyl disaster. According to the Soviets (20), the 24,000 persons between 3 and 15 kilometers from the plant, but excluding the town of Pripyat, received and are expected to receive 1.05 million man-rems total integrated dose, or about 44 rems average. Even if we assume a linear dose-response relation, with 8000 man-rems per cancer, the risk may be expressed in different ways. Dividing 1.05 million man-rems by 8000 gives 131 cancers expected in the lifetimes of that population. This is larger than, and for some people more alarming than, the 31 people within the power plant itself who died within 60 days of acute radiation sickness combined with burns. Dividing the 131 again by the approximately 5000 cancer deaths expected from other causes, the accident caused "ordy" a 2.6% increase in cancer. This seems small compared to the 30% of cancers attributable to cigarette smoking. The difference is even more striking if we consider the 75 million people in Byelorussia and the Ukraine who received, and will receive, 29 million man-rems over their lifetimes. On the linear doseresponse relation this leads to 3500 "extra cancers," surely a large number for one accident. But dividing by the 15 million cancers expected in this population leads to an "insignificant" increase of 0.023%. Of course, none of the methods of expressing the risk can be considered "right" in an absolute sense. Indeed, it is our belief that a full understanding of the risk involves expressing it in as many different ways as possible.

Cost of Reducing a Risk

Another interesting and instructive way of comparing risks is by comparing the amount people have paid in the past to reduce them. It might be thought that people would try to adjust their activities until the amount spent is roughly the same. Cohen (21) has shown that the amounts spent vary by a factor of more than a million. He shows that it would be possible even for an American to save lives in Indonesia by aiding in immunization at \$100 per life saved. Society is willing to spend more on environmental protection to prevent cancer (over \$1 million per life) than on cures (about \$50,000 per life with the high value of \$200,000 for kidney dialysis raising some objections). This ratio is in rough accord with the maxim "an ounce of protection is better than a pound of cure." People are willing to spend still more on radiation protection at nuclear power plants and

Table 3. Comparison of two very toxic chemicals, aflatoxin B1 (22) and dioxin (23); CDC, Centers for Disease Control.

| Aflatoxin B1 | Dioxin |
|--------------|--|
| High | Equal |
| ~500 | Unknown |
| ~5000 | ~5000 |
| Yes | No |
| High | Low |
| Initiator | Promoter (?) |
| Low | High |
| Natural | Artificial |
| Little known | Agent Orange |
| 20 | |
| | l |
| | High ~500 ~5000 Yes High Initiator Low Natural Little known |

on waste disposal. Economists and others often argue that efficiency depends on adjusting society until the amounts spent to save lives in different situations are equalized. It seems to us that society does not work that way. People are aware of the order of magnitude of these differences, and approve of them. Nonetheless, we believe that providing this information to a decision-maker is essential for an informed decision.

REFERENCES AND NOTES

- L. B. Lave, Science 236, 291 (1987).
 R. Wilson, E. A. C. Crouch, L. Zeise, in Risk Quantitation and Regulatory Policy (Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY, 1985), Banbury
- (Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY, 1985), Banbury Report, vol. 19, pp. 133–147.
 3. N. C. Rasmussen et al., "Reactor safety study—an assessment of accident risks in U.S. commercial nuclear power plants" (WASH 1400, NUREG 75/014, U.S. Nuclear Regulatory Commission, Washington, DC, 1975). See also D. Okrent, Science 236, 296 (1987).
 4. R. Doll and R. Peto, J. Natl. Cancer Inst. 66, 1191 (1984).
 5. E. L. Anderson et al., Risk Anal. 3, 277 (1983).
 6. E. A. C. Crouch and R. Wilson, J. Taxicol. Environ. Health 5, 1095 (1979).
 7. E. J. Calabrese, Principles of Animal Extrapolation (Wiley, New York, 1983).
 8. P. Peto, in Assessment of Risk form Lowel Exposure to Radjation and Chemicals.

- E. J. Calabrese, Frinciples of Animal Extrapolation (Wiley, New York, 1988).
 R. Peto, in Assessment of Risk from Low-Level Exposure to Radiation and Chemicals, A. D. Woodhead, C. J. Shellabarger, V. Pond, A. Hollaender, Eds. (Plenum, New York, 1985), pp. 3–16.
 B. N. Ames, R. Magaw, L. S. Gold, Science 236, 271 (1987).
 "Control of trihalomethanes in drinking water," proposed rule, Fed. Regist. 43, 5756 (1968). See also the advanced notice [ibid. 41, 28991 (1976)] and the final rule [ibid. 44, 68624 (1979)].
- rule [ibid. 44, 68624 (1979)]

- Tule [ibid. 44, 68624 (1979)].
 M. Meselson and K. Russell. in Origins of Human Cancer. H. H. Hiatt, J. D. Watson, J. A. Winsten, Eds. (Cold Spring Harbor Laboratory, Cold Spring Harbor, NY, 1977), p. 1473.
 S. Parodi, M. Taningher, P. Boero, L. Santi, Mutat. Res. 93, 1 (1982).
 L. Zeise, R. Wilson, E. A. C. Crouch, Risk Anal. 4, 187 (1984).
 Smoking and Health, a Report of the Surgeon General (PHS79-50066, Public Health Service, Washington, DC, 1979).
 R. A. Squire, Science 214, 877 (1981).
 "Saccharin and its salts," proposed rule and hearing, Fed. Regist. 42, 19996 (1977).
 R. Wilson and W. J. Jones, Energy, Ecology and the Environment (Academic Press, New York, 1974), table 9-6. Other entries may be readily calculated from data in the reports of the United Nations scientific committee on the effects of atomic radiation ["Sources and effects of ionizing radiation" (United Nations, New York, 1977)] and the report of the Committee on the Biological Effects of Ionizing Radiations ["The effects on populations of exposure to low levels of ionizing radiations" (National Academy Press, Washington, DC, 1980)].
 M. Russell and M. Gruber, Science 236, 286 (1987).
 A. Tversky and D. Kahneman, ibid. 211, 453 (1981). See also P. Slovic, ibid. 236, 286 (1987).

- U.S.S.R. State Committee for the Utilization of Atomic Energy, "The accident at the Chernobyl Nuclear Power Plant and its consequences," working document for the Post Accident Review Meeting, 25–29 August 1986, International Atomic
- Energy Agency, Vienna.
 B. L. Cohen, Health Phys. 38, 33 (1980).
 H. R. Roberts, "The regulatory outlook for nut products," paper presented at the Annual Convention of the Peanut Butter Manufacturers and Nut Salters Association, West Palm Beach, FL, November 1977.
 R. D. Kimbrough, H. Falk, P. Stehr, G. Fries, J. Toxicol. Environ. Health 14, 47 (1984)
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270 SCIENCE, VOL. 236 "ANY POLITICIAN WOULD PREFER A
DEAD BODY TO A FRIGHTENED VOTER"

-- JOHN DUNSTER,
U. K. HEALTH AND
SAFETY INSPECTOR

SURVEY FOR MARSH-MCLENNON

Question: Thinking about the actual amount of risk facing our society, would you say that people are subject to more risk today than they were 20 years ago, less risk today, or about the same amount of risk today as 20 years ago?

| Level of risk | Percent of responses | | | | | |
|---------------|---|--------------------------------|---------------|-------------------------------|----------------|--|
| | Top corporate executives (401) | Investors/ Lenders (104) | Congress (47) | Federal regulators (47) | Public (1,488) | |
| More risk | 38 | 60 | 55 | 43 | 78 | |
| Less risk | 36 | 13 | 26 | 13 | 6 | |
| Same amount | 24 | 26 | . 19 | 40 | 14 | |
| Not sure | 1 | 1 | | 4 | 2 | |

Question: Would you say that people are subject to more risk today than they were 20 years ago, less risk today, or about the same amount of risk today as 20 years ago?

| | Percent of responses | | | | |
|---|-----------------------|------------------|--------------|----------------|-------------|
| Demographic characteristics | Number of respondents | More risk | Less risk | Same amount | Not sure |
| Sex | | | | | |
| Male Female | 702 7 8 6 - | 74 82 | 10 2 | 15 14 | 2 2 |
| Age 55 and over | 179 | 86 | 2 | 10 | 2 |
| Education Not high school graduate | 268 · | 85 | 3 | 9 | 3 |
| Marital status Separated, divorced, widowed | 226 | 82 | 2 | 13 | 3 |
| Household income \$7,500 or less | 211 | 83 | 4 | 10 | 3 |
| Race White Black | 1,258 155 | 77 \$8 | 6 3 2 | 15 | 2 2 |
| Spanish-American Total | 37 1,488 | 8 4 78 | 6 | 7 | 2 |

[&]quot;Source: Marsh & McLennon Co., Inc. Risk in a complex society: A public opinion survey.

ANumbers in parentheses indicate number of respondents in each category.

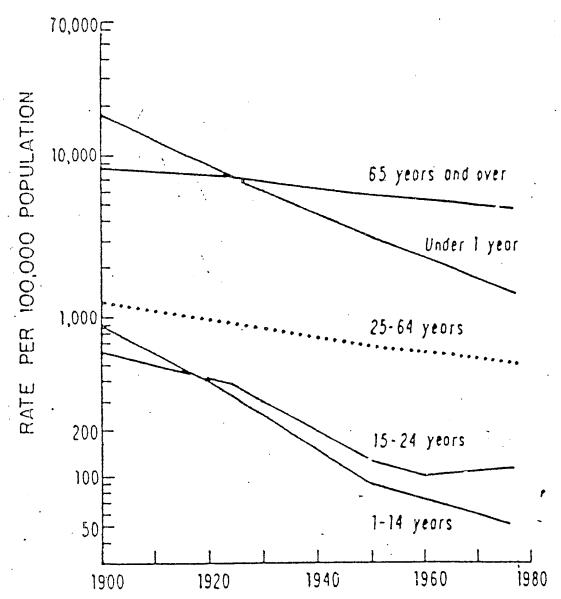
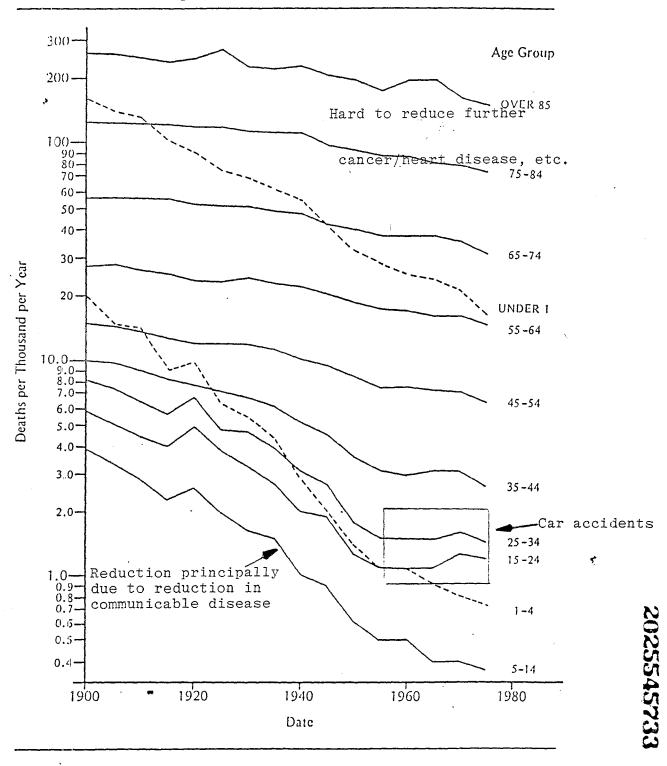
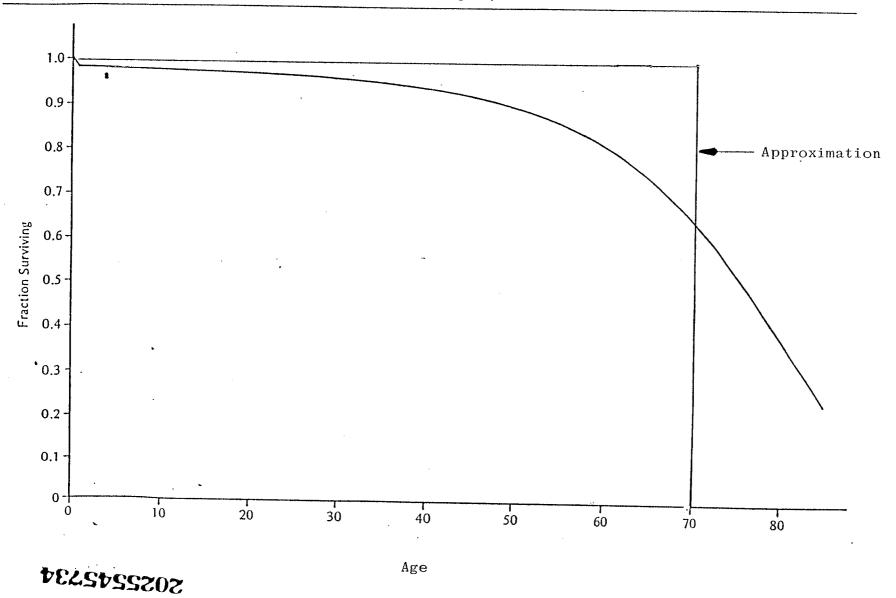
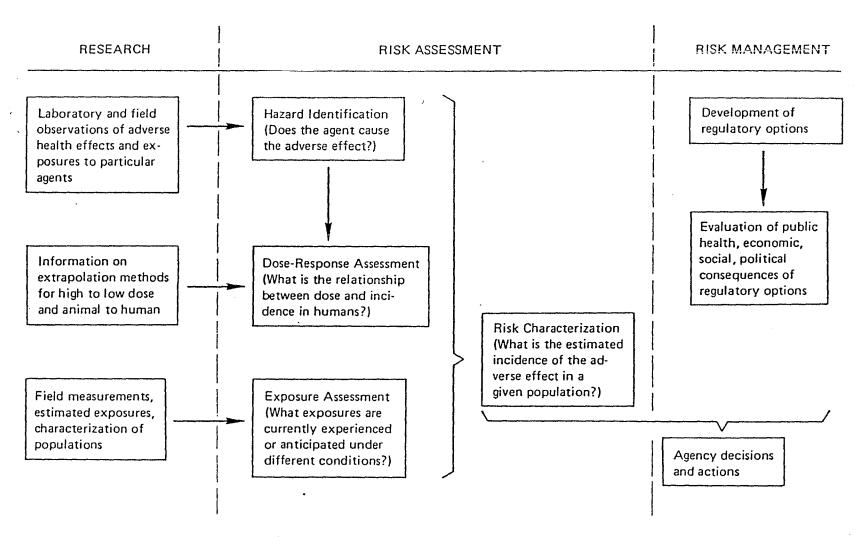


Figure 1. Death rates by age in the United States, for selected years, 1900–1977 (from the U.S. Department of Health, Education and Welfare statistics).

Death Rates at Five Year Intervals from 1900 to 1975 for Various Age Groups: United States.



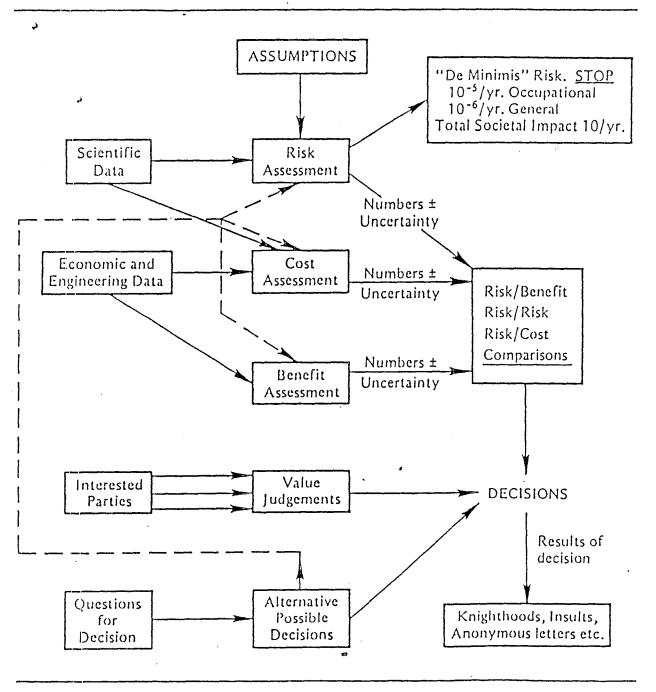




Elements of risk assessment and risk management.

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Idealised Scheme for Risk Analysis.



RISK = PROBABILITY OF OCCURRENCE x SEVERITY OF EVENT

RISK UNITS:

DEATHS/YEAR

DEATHS/TON OF COAL (BTU, khw)

DEATHS/WORKING MAN

LOSS OF LIFE EXPECTANCY

WORKING DAYS LOST (WDL)

PUBLIC DAYS LOST (PDL)

RISK <---> UNCERTAINTY

If I am certain I will die of cancer,
I do not describe it by the word RISK.

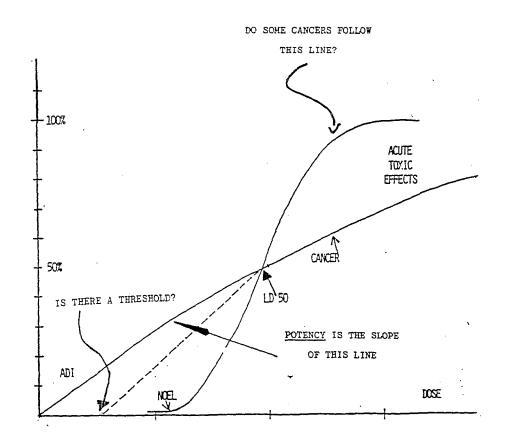
Risk changes as information improves either as events develop by study

Use of the word risk implies that there is uncertainty.

When there is uncertainty there remains a risk.

2. STOCHASTIC
Will this particular car kill me?
Or pass me by?
Will this particular carcinogen give me cancer?

(One-third of cigarette smokers die of their habit we do not know, and probably never will know, which)



CERTAINTY OF INFORMATION WITH MAGNITUDE OF RISK

E.g. Vinyl Chloride

- o Human carcinogen
- o Mutagen (with activation)
- o Animal carcinogen

May be initiator, i.e. linear dose-response
BUT only 130 angiosarcomas from 30 years exposure worldwide; perhaps

- 70 more from past exposures
- 200 other cancers from past exposures
- 130 from 30 years exposure worldwide
- 400 TOTAL over 30 years worldwide

MOREOVER, EXPOSURES NOW DOWN 1000-FOLD SO WE EXPECT < 1/60 YR IN THE FUTURE

RISK OF A NEW CHEMICAL

ARDENT ENVIRONMENTALIST --> 1 (because we don't know that it is safe)

MYOPIC INDUSTRIALIST --> 0
(because we don't know that it is dangerous)

The job of a RISK ASSESSOR is to find a number

in between with its uncertainty

1 > R > 0

*

*
* FIRST RULE: WHENEVER THERE IS DATA ON HUMANS -- USE THEM *

CIGARETTES STUPIDITY

NAPTHALYAMINE OCCUPATIONAL

BENZIDINE OCCUPATIONAL

ARSENIC -- Inhalation OCCUPATIONAL

-- Ingestion OCCUPATIONAL

BENZENE OCCUPATIONAL

AFLATOXIN B; FOOD

RADIATION WAR

(Monson will discuss how epidemiology works)

THERE IS NEGATIVE EPIDEMIOLOGY

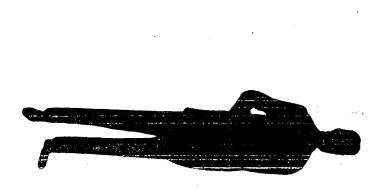
PEOPLE HAVE BEEN EXPOSED BUT THERE IS NO SIGN OF AN EFFECT

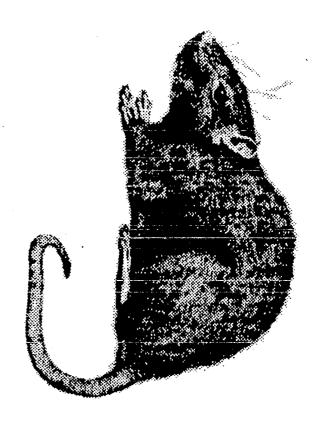
E.G. There is no firm evidence that unleaded gasoline in a refinery causes cancer.

Therefore normal users of gasoline, with lower exposure, have less risk.

The two assumptions made (in using human epidemiology) are:

- EXPOSURE in the situation being assessed is similar to that of the epidemiological study
- 2. The DOSE-RESPONSE RELATION must be assumed,
- since we need risk at low doses





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PROPORTION OF CANCER DEATHS ATTRIBUTABLE TO DIFFERENT FACTORS

Per cent of all cancer deaths

| Factor or class of factors | Best estimate | Range of acceptable estimates |
|----------------------------------|-------------------|-------------------------------|
| Cigarette smoking | 25 | 20 to 30 |
| Alcohol | · 3 | 2 to 4 |
| Diet | _{. ,} 35 | 10 to 70 |
| Food additives | >1 | -5* to 2 |
| Reproductive and sexual behavior | 7 | 1 to 13 |
| Occupation | 5 | , 2 to 10 |
| Pollution | 1 | >1 to 3 |
| Industrial products | >1 | >1 to 2 |
| Medicines and medical procedures | 2 | 1 to 3 |
| Geophysical factors+ | 3 | 2 to 3 |
| Infection | 3 | 1 to ? |
| Unknown | ? | ? |

Source: R. Doll and R. Peto, J. Natl. Cancer Inst. 66, 1191 (1984).

REASONS FOR CHOOSING RATS AND MICE FOR EXPERIMENTS

They are easy to breed.

They are mammals and have some similarity in metabolic processes to man.

They live only two years so that an experiment can be completed within a human lifetime.

PETO ARGUMENT

- IF ALL TISSUES ARE EQUAL WHETHER ATTACHED TO MOUSE OR MAN,
 WE EXPECT BILLIONS MORE CANCERS IN MAN THAN MOUSE
 - 1. CANCER INCREASES WITH WEIGHT (M)
 - 2. CANCER IS KNOWN TO VARY AS A HIGH POWER OF AGE (\mathtt{T}^4)
 - . . At the end of life the ratio of cancer in man to cancer in mouse for equal daily intake (roughly proportional to mass x time)

$$\left(\frac{M_{\text{man}}}{M_{\text{mouse}}} \times \frac{T_{\text{man}}}{T_{\text{mouse}}}\right) \left(\frac{T_{\text{man}}}{T_{\text{mouse}}}\right)^{4} = \frac{70 \text{ kg}}{30 \text{ kg}} \times \left(\frac{70}{2}\right)^{4}$$

SEVERAL BILLION!

BUT WE KNOW IT IS CLOSER TO 1 BECAUSE

- (i) of background
- (ii) of experiment

SO THE METABOLISM MUST ACCOUNT FOR A FACTOR OF A BILLION

(Calabrese will discuss)

E.g. Vinyl Chloride

- o Human carcinogen
- o Mutagen (with activation)
- o Animal carcinogen

May be initiator, i.e. linear dose-response

BUT only 130 angiosarcomas from 30 years exposure worldwide; perhaps

- 70 more from past exposures
- 200 other cancers from past exposures
- 130 from 30 years exposure worldwide
- 400 TOTAL over 30 years worldwide

MOREOVER, EXPOSURES NOW DOWN 1000-FOLD

SO WE EXPECT < 1/60 YR IN THE FUTURE

CONTRAST WITH SACCHARIN

Wide use; if dose-response is LINEAR, FDA calculate 500 cancers/year (April 15, 1987 Federal Register) (x 10^{\pm} uncertainty)

But dose-response relation may be non-linear Not found in humans (sensitivity too small)

Not a mutagen

ILLUSTRATIVE CATEGORIZATION OF EVIDENCE BASED ON ANIMAL AND HUMAN DATA¹

| | Animal Evidence | | | | | |
|----------------|-----------------|---------|------------|---------|-------------|--|
| Human Evidence | Sufficient | Limited | Inadequate | No Data | No Evidence | |
| Sufficient | A | A | A | A | A | |
| Limited | Bl | Bl | Bl | Bl | Bl | |
| Inadequate | B2 | С | D | D | . D | |
| No data | В3 | С | D | D | E | |
| No evidence | B4 | С | D | D | E | |
| | | | | | | |

Source: Fed. Reg. <u>51</u>, No. 185, Wednesday, Sept. 24, 1986.

The above assignments are presented for illustrative purposes. There may be nuances in the classification of both animal and human data indicating that different categorizations than those given in the table should be assigned. Furthermore, these assignments are tentative and may be modified by ancillary evidence. In this regard all relevant information should be evaluated to determine if the designation of the overall weight of evidence needs to be modified. Relevant factors to be included along with the tumor data from human and animal studies include structure-activity relationships, short-term test findings, results of appropriate physiological, biochemical and toxicological observations, and comparative metabolism and pharmacokinetic studies. The nature of these findings may cause an adjustment of the overall characterization of the weight of evidence.

CRITICAL COMMENTS BY DISTINGUISHED PEOPLE ON RISK ASSESSMENTS FOR CARCINOGENS

*RICHARD PETO, Reader in Epidemiology, University of Oxford:

All important carcinogens found by epidemiology; none by animal tests

All that can be done is form a priority list

Some index of nastiness

N

Some index of exposure

 \mathbf{E}

Prioritize by N x E

Use more than one index to be sure that nothing is missed

*in Assessment of Risk from Low-Level Exposure to Radiation and Chemicals eds., A.D. Woodhead, et al., (Plenum, New York), 1985.

**AMES (Professor of Biochemistry, U.C. Berkeley) AND OTHERS

Prepare a priority list from animal tests

**Science, <u>236</u>, 271 (1987).

DOUGLAS FOY, (lawyer for Conservation Law Foundation)

Although risk numbers are not believeable, they are useful as a priority list

AHMED (Environmental Defense Fund)

Statement similar to Foy's

CONCLUSION:

A CALCULATED RISK OF A SINGLE CHEMICAL BY ITSELF IS NOT USEFUL

ONE NEEDS A LIST OF SEVERAL

FDA Approach to Risk Assessments

Scheuplein

RISK ASSESSMENT OF CHEMICAL CARCINOGENS:

IS IT TIME FOR A CHANGE?

Ву

Robert J. Scheuplein, Ph.D.
Director, Office of Toxicological Sciences
Center for Food Safety and Applied Nutrition
Food and Drug Administration
Washington, D.C. 20204

Thank you, Carol, for the introduction and to ILSI for inviting me to speak to you today.

My subject is the Quantitative Risk Assessment of Carcinogens: Is it time for a change? Before I speculate about the direction in which risk assessment might be headed or ought to be turned, I would like to give you some idea of where I think its come from, what science it rests on, what it is and what it is not.

This will involve a brief scientific history of cancer risk assessment with a few detours to places where it touches social policy or has been influenced by the Congress and the regulatory agencies. This interaction between science and regulation is important to understand, because a part of my thesis will be that despite well over 500 papers on cancer risk assessment, on the bioassay, on cancer thresholds and numerous related subjects, since 1961 (the date of Mantel and Bryan's paper) -- cancer risk assessment is still more of a regulatory tool than a scientific discipline and rests more on regulatory need than scientific plausibility.

Presented at Brookings Institution, Washington, D.C. June 17, 1991

It nonetheless involves several scientific matters and any good history should include them: (Slide 1) - Major Scientific Issues in Cancer Risk Assessment.

These issues are all involved in QRA and the final result - the determination of a safe level - depends on how these issues are resolved. And I'll touch briefly on most of them.

Right after World War I, scientists began to experiment with large colonies of rodents. Shortly thereafter, Yamagiwa and Ichikawa discovered that skin cancers could be induced in mice by the repeated application of gas tars (ref.). The number of chemical agents tested grew steadily from year to year and it became difficult to analyze the available experimental results because of the variety of different methods adopted. By 1930, efforts began at standardizing these methods. (Slide 2) - Paper Title by Twort and Twort.

By 1939, methods were sufficiently well developed that lists of substances with relative potencies were published based on the ability of a compound's capacity to produce tumors in the shortest possible time.

(Slide 3) - List of Carcinogenic Compounds Arranged in Descending Order of Fotency - John Iball (1939). In this list by John Iball in 1939, the index of potency is the percentage of tumours A divided by the mean latent period B, recorded in the last column.

There were good social reasons for these academic efforts. It was becoming clear that environmental and occupational exposure to

carcinogenic chemicals were contributing to the world-wide diversity in cancer incidence. Percival Pott had established the connection between soot and scrotal cancer in chimney sweepers several generations earlier. By the 20's it was clear that polycyclic hydrocarbons were the carcinogenic ingredients in soot, tar and oil. Some cancers on the abdomen could be attributed to carrying a basket of live coals beneath the clothes to keep warm in winter; some cancers in the buccal cavity could be attributed to chewing various mixtures of betel, tobacco and lime and some on the palate to smoking cigars. As Richard Doll (1977) has pointed out, oncologists who worked chiefly in Europe and North America tended to regard these incidents as oddities and irrelevant to the production of ordinary cancers. So it took a while for people to associate the majority of cancers with environmental factors, but soon the association became obvious.

These concerns in the 30's and 40's motivated an effort to bring the known occupational hazards under control, either by banning their production or controlling the manufacturing process to reduce exposure to employees. (Slide 4) - Occupational Cancers - Doll (1977). But these occupational hazards could not be responsible for the large observed incidence of cancer. Whole populations, however, had been exposed to lower levels of these same agents. These included polycyclic hydrocarbons, produced by the combustion of coal, wood and oil. It was known, for example, that residents of large towns in the U.K. may have been exposed - mainly through the combustion of domestic coal - to something like 1/100 the amount of benzo(a)pyrene regularly inhaled by men working in the manufacture of coal gas and these men experienced only

an 80% excess risk of lung cancer (Doll, et al, 1972). It was easy enough to dismiss the corresponding risks on the grounds that the doses were minute, but one did not then (or now) assume for cancer the existence of a threshold. So some form of quantitative relationship between the dose and the resulting incidence was needed. But in the absence of such a relationship, decisions had to be made and FDA banned carcinogens from food during the years well prior to the enactment of the Delaney Clause. Arnold Lehman, the chief toxicologist at FDA in the 40's, stated in an article in 1949 that:

"a finding that a substance caused cancer in animals was regarded as so 'alarming' as to exclude it from consideration."

In 1945, the FDA banned Butter Yellow; in 1950 Dulcin and P-4000, two artificial sweeteners; in 1950 also tonks beans and coumarin; and in 1959, aminotriazol on cranberries, all on the grounds they were carcinogens and had no place in foods.

The reasons that scientists were unwilling to assume the existence of thresholds for carcinogens are interesting - primarily because they were largely theoretical. Essentially the argument recast in modern terms went like this: Cancer is caused by agents known to be mutagenic suggesting that at least one crucial, rate limiting step is a somatic mutation. This focused attention on the nature of the genes that undergo mutation and on the amount of chemical needed to affect that change. It was argued that only one molecule was necessary to produce a mutation in the DNA within the nucleus of a cell. This in turn could lead to a

miscoding sufficient to produce eventually a malignant cell. The cell then can reproduce itself in an irreversible and unregulated manner to yield a malignant tumor.

But this is theory! What does the experimental evidence show? So far, for amy carcinogenic or mutagenic response in any given situation, be it man, mouse, isolated organ or a Salmonella plate assay, there is a demonstrable threshold or "no effect level." In thousands of studies with hundreds of thousands of animals, not a single carcinogen has been found that has not exhibited an experimental threshold. However, animal studies are insensitive and thresholds will vary from individual to individual. It is completely impractical to determine the level at which the most susceptible individual in the whole population might fail to respond. And worse yet, if a gargantuan animal study were done, assuming all the experimental difficulties involved in such a study could be overcome, people would point out that experimental animals are more inbred than people and the result would probably be discounted.

The one-molecule theory has to be argued at the theoretical level, so let's look at it. Nothing (in the one-molecule theory) is mentioned about the relationship between the intake dose and the final concentration of the chemical carcinogen in the nucleus of the cell where it interacts with DNA. Substances that are ingested have to be absorbed, distributed and metabolized usually before they can reach critical organs in chemically activated form. Then the activated molecules have to run a gauntlet of sequestration by other uninvolved macromolecules and overcome

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diffusional barriers before they can first enter a cell, and then later enter the nucleus of a cell.

When the carcinogen is in the nucleus and poised to react with DNA, nothing is mentioned (in the one-molecule theory) about the constraints imposed on chemical reactions by the requirements of mass action or the need to acquire a transition state configuration or an activation energy prior to reaction, or even that the final adduct be somewhat stable so that it can last long enough for replication.

And if a reaction with DNA does occur, nothing is mentioned about the intron content of the DNA, that the amount of DNA in the nucleus that is not overtly expressed as protein may amount up to 90% of the total.

These regions of DNA, which correspond mostly to the centromeric parts of the chromosomes almost certainly instruct no other process than their own replication. And finally nothing is said of the ability of the organism to accommodate to adverse effects — in this case by DNA repair mechanisms and enzyme induction. An example on this last point was published in 1977 by Tony Pegg of the Hershey Medical Center.

Dimethylnitrosamine (DMN) is a potent carcinogen in many species. It is well established that DMN exerts its carcinogenic effect after its metabolic conversion into a reactive methylating agent. The electrophile then methylates DNA nucleosides which are likely to miscode. One particular adduct -0^6 - methylguanine appears to be promutagenic or tumorigenic in several studies and it has been identified as probably the adduct responsible for tumor induction in animals.

What Pegg did was to give DMN to rats and then analyze the livers for the 0^6 -adduct after 4 and 24 hours. His results are shown in the slide. (Slide 5). 0^6 -Methylguanine Levels in Rat Liver DNA At first glance, there appears to be a linear relationship between the administered dose and the formed adduct. But if the data are extended to lower doses, this is shown not to be true. At very low doses, 0^6 -adducts levels are many times less than expected on the basis of linearity. Later studies showed that a saturable enzymic repair system was responsible for the removal of the 0^6 -adduct and that the repair system operated in both liver and kidney cells.

These studies don't necessarily imply an absolute threshold for tumor induction for DMN because it was possible to detect some 0^6 - adduct in DNA 24 hours after a single dose and we don't know what level of 0^6 -methylguanine may be necessary to initiate tumor induction. But they do show that liver and kidney can protect itself against a low-dose, carcinogenic stimulus and that linear extrapolation is probably unjustified at low doses. These studies by Pegg are pertinent because they provide information well below the observable tumorigenicity range - over a 20,000 fold dose range - and measure the concentration of the specific adduct identified to be the one likely to initiate tumors.

In summary, there are many reasons to contest the "one-molecule theory" and to anticipate, in conformity with the animal evidence, that significant concentrations of a carcinogen might be required to elicit cancer. But nevertheless, the "one-molecule" concept or its equivalent that exceedingly small levels of carcinogens ingested daily for a lifetime

could be harmful, prevailed - in the 40's and 50's, and I suspect prevail today. Now the question of the existence of a threshold in an individual is a problem in biology - the question of determining the range of possible susceptibility in a large population that is assumed to have individuals capable of responding is a problem in the statistics of sampling to which we now turn.

We have to skip over (in the interests of time) a rich part of the biological science that was developed in the 40's and 50's to arrive at our principal focus, the idea of using risk assessment for setting safe population exposure levels for carcinogens, This idea was first published, so far as I am aware, by Mantel and Bryan in 1961.

They showed that a negative animal study - particularly a small one with 100 animals or so, does not necessarily demonstrate that the treatment was safe. Studies of feasible size can be used to establish directly only risks of the order of 1/100 or higher. When a study with 100 animals is negative, we can only claim that we are reasonably sure (assurance level of 99%) that the true risk is no greater than 4.5 percent. (Slide 6) - Interpretation of Negative Studies. Mantel and Bryan then proposed to rely on the dose-response principle and extrapolate from this upper limit conservatively to human exposure levels. They examined the dose-responses of many chemicals and concluded that most chemical responses involving lethality decreased very rapidly, with dose-response slopes steeper than 10 or more probits per ten-fold dose dilution. They noted probit slopes for the therapeutic effects of antibiotics of 2-3, and still lower probit slopes, the order of 2, in

virus assay work. From this experience they felt that a probit slope of one per ten-fold dose dilution would likely be quite conservative for carcimogens. This would mean in the example above that the safe dose corresponding to a risk of 1/100 million would be 1/8,300th of that which produced no tumors in the actual study.

This 8,300 corresponds to a safety factor based on an upper confidence limit to a negative study. Later Carrol Weil would propose a factor of 5000 for known carcinogens, using a factor of 10 for animal variation, a factor of 10 to translate animal results to human, a factor of 10 for cancer on the theory that it is less reversible than other toxic effects and a factor of 5 if the data used were a minimum effect level. (Weil 1972).

The Delaney Clause had been passed by Congress a few years earlier as part of the Food Additives Amendment in 1958. In 1960, there were hearings in the House to deal with some unfinished business regarding Color Additives. Cancer experts testified to the Committee that there was a great deal of uncertainty about cancer induction at low doses. A report prepared by G. Burroughs Mider, then Associate Director for Research at NCI, was quoted by the Secretary of HEW at the hearings. It had an impact on the Committee. It stated:

"No one at this time can tell how much or how little of a carcinogen would be required to produce cancer, or how long it would take the cancer to develop."

The Secretary also said,

"Whenever a sound scientific basis is developed for the establishment of tolerances for carcinogens, we will request the Congress to give us that authority."

and also,

"So long as the outstanding experts in the National Cancer Institute and the Food and Drug Administration tell us that they do not know how to establish with any assurance at all a safe dose in man's food for a cancer-producing substance, the principal in the anticancer clause is sound."

The Congressional response was, of course, predictable and the new Color Additives Amendments of 1960 contained its own Delaney anticancer clause. Congress concluded that there was too much uncertainty and it would require FDA to regulate on the side of caution by banning all animal carcinogens from the food supply. Of course, it was only 1960 - analytical methods were typically capable of detecting a few parts per million at best. There were relatively few carcinogens known and it was not appreciated that traditional food and spices and ordinary cooking practices would eventually be found to account for many if not most of them. The widespread contamination of food by low levels of environmental contaminants like dioxins, PCBs and aflatoxin had not yet been discovered. Nor was the fact that the failure to specify "safe" levels would assure the triggering of the Delaney Clause on food and color

additives as methods improved to the point of being capable of detecting trace carcinogenic contaminants.

This was the scientific and regulatory setting when in 1969 the FDA gathered together a group of scientists to consider how food additives and pesticides should be tested and evaluated for possible carcinogenicity. The Report of that FDA Advisory Committee on Protocols for Safety Evaluation and in particular the Panel on Carcinogenesis was published in 1971.

This report stated among other things that:

- Testing should be done at doses and under experimental conditions
 likely to yield maximum tumor incidence;
- 2) And that at least two species should be used for all carcinogenicity tests, and that,
- 3) For compounds judged carcinogenic at test levels, a virtually safe dose could, in principle, be estimated by downward extrapolation using some arbitrarily selected but conservative dose-response curve.

These recommendations initiated the regulatory use of the MTD bioassay and Ilnear risk assessment. Details on both the bioassay and the method of extrapolation would evolve, but this 1971 Panel Report gave their

development official sanction. The Panel's recommendations were motivated essentially by two concerns -

- 1) the fears over persistent low doses of carcinogens in food
- 2) the limitations of negative studies on small numbers of animals

It was clear that no unqualified negative answer is ever possible. That all a negative study can do is to supply an upper limit to the possible carcinogenicity. It was pointed out that these upper limits are uncomfortably large. Even with as many as 1000 test animals and using only 90% confidence limits, the upper limit yielded by a negative experiment is 2.3 cancers per 1000 test animals.

The report contains the following statement:

"No one would wish to introduce an agent into a human population for which no more could be said that it would probably produce no more than 2 tumors per 1000."

So how does one increase the sensitivity of the bioassay with a limited number of animals? The answer - increase the dose well beyond the anticipated use level and extrapolate the results down to these low doses. If the study is positive, the fidelity of the extrapolation depends on the dose-response curve - a small part of which is accessible in the experimental range. And if the study is negative, it has a theoretical positive upper bound.

Mantel and Bryan had already introduced the concept of using this upper limit of the negative study to base the downward extrapolation on, using a 1 probit per 10 fold dilution slope. And so, in principle, quantitative extrapolation as a regulatory method (QRA) was approved.

But it was never assumed that cancer necessarily occurred at low doses, but only that if it did, it would be safely bounded by the extrapolation procedure. Now extrapolating a positive response instead of an upper limit to a negative response makes no essential difference as Starr and others have shown unless we know what the dose response curve is. Since our extrapolation models are quite simplistic and without an adequate biological basis — there need not be any cancer at all at low doses — and if there is, we have no idea about its actual dose response. The notion that one can calculate expected values of an actual risk from such an analysis is really quite bizarre. Extrapolation using bioassay data 3-4 orders of magnitude removed is not a procedure for estimating risk — it's regulatory standard setting — It's not science, it's policy. And it's conservative or, if you will, prudent policy — and I'm just describing it, not advocating it.

The scientists who wrote the 1971 Protocols Report had to face two problems. The QRA procedure they were recommending was extremely conservative, it would ban any carcinogenic food additive, because the amount of additive is usually substantial. Remember the additive has to be used in amounts sufficient to accomplish its intended effect. But this didn't really bother anyone at the time - carcinogenic additives had no place in food anyway. And they pointed out that this application of

QRA would be consistent with the Delaney Clause. They didn't think back then in terms of impurities and low level environmental contaminants — and if they had, I don't think they would have recommended high to low dose extrapolation. I believe this is true because of how they handled the second problem.

If you tested a food additive in a carcinogen bloassay and the result was negative, the logical result of their analysis would require a downward extrapolation from the upper 90% confidence limit ala Mantel and Bryan. But again, because of the substantial amount of food additive required for a functional effect - typically at least several ppm, this extrapolation would ordinarily result in the ban of the additive at effective and useful doses. What did they do?

They ignored their discussion on QRA, they ignored Mantel and Bryan and said that the sensible thing to do was to use a 100-fold safety factor! Their statement was that for agents not judged carcinogenic the use of QRA to estimate a safe dose would be logical, but would give a level so low as virtually to exclude from use agents for which there was no positive evidence of carcinogenicity. And they wouldn't do it.

This commonsense approach to the cancer problem was soon to be challenged by two related difficulties that defied easy solution. The first was how to deal with animal drug residues - those in food-producing animals as the result of ingestion of added drugs for prophylaxis, for the treatment of disease or for growth promotion. In 1962, Congress had put yet another Delaney Clause in the Act with the Animal Drug Amendments - this

time though with a legal loophole called the DES Proviso. It said in effect that you could use effective animal drugs even if they were carcinogenic so long as none remained in the edible tissue of the animal after slaughter - no residue would be permitted and the FDA was given the task of approving the analytical method to assure it. This ushered in the era that some industry groups characterized as "chasing zero."

The other related difficulty occurred in food and color additives. Analytical methods were becoming so sensitive that traces of carcinogenic contaminants were being found, particularly in colors. It was hard not to find carcinogenic derivatives of aniline, a carcinogen, in aniline-based colors. And so the question was how do you regulate a substance which does not test out as a carcinogen itself, but which contains a chemical at low but detectable levels which is a known carcinogen? Both of these problems would challenge FDA for many years, the first culminating in the final SOM document in 1985, the other in the constituents policy in 1983. The need for both a procedure for risk assessment and a level of acceptable risk were common to both issues and of course they are interrelated. If you use the Probit model and a 10⁻⁸ acceptable risk level, you come out about the same place as if you used a linear model and a 10⁻⁶ acceptable risk level.

Extrapolation Models and Background Additivity

In the late 70's and early 80's, there was a good deal of debate over the best form of the extrapolation model. The original <u>Probit</u> model of Mantel and Bryan was considered too arbitrary and not conservative enough — with the developing trend toward a 10⁻⁶ or one in a million

theory and was easier to explain, but it wasn't a good fit for most data. There were other models. You may recall the Logit, the Weibull, the Multihit and the Gamma Multi Hit - all of them competing with the Multi-Stage. None of these were based on biology. The critical steps and mechanisms in the development of tumours were and are still unknown. But the multistage model had the best biological credentials, having first been used to explain the steep increase in the age adjusted rates of some cancers in humans by Armitage and Doll in 1961. And most people believed cancer was a multistage process, so there was a simulacrum of a biological basis. Since the early 80's, the strongly curvilinear models have virtually been abandoned. What was that? Well, first the low level risks that emerged from these different models were embarrassingly divergent. When the various models were applied to the risk of saccharin by the NAS in 1978, the risk estimates ranged over 5 million.

(Slides 7 and 8) - Saccharin Risk Estimates (1978).

If OMB had been paying attention back then, they would have been exultant - this risk assessment certainly made the uncertainties in modelling crystal clear! Today our risk assessments don't differ very much. EPA ordinarily uses the <u>Multistage</u> with an algorithm that constrains it to be linear and FDA uses the <u>Gaylor-Kodell</u> procedure for most carcinogens, which is designed to be linear. The other models could not be easily linearized and were abandoned. Since then our risk assessments have been more nearly in agreement, more uniformly conservative and much less revealing of still unresolved uncertainties. The linear multistage

yielded greater conservatism and had the right name, but what really clinched linear risk assessment was an idea published in 2 or 3 papers in 1977 and 1978 by Crump, Hoel, Peto and their co-workers. These papers contained a notion which today is unfortunately part of quantitative risk assessment mythology, namely that there are sound biological reasons for believing that every carcinogen response curve is linear at low dose rates, as far as humans are concerned. This proposition rests on the presence of background carcinogens and the way they interact with the carcinogen in question. The reasoning is part biological and part mathematical.

The biological part

Approximately one of five Americans develops a cancer, and every person is exposed to thousands of carcinogens in food, in the environment and even endogenously. This 20% background rate, from these many different chemicals must surely provide some significant mechanisms that are shared by the carcinogen in question. In other words, the carcinogen being added and some of the background carcinogens must share a common pathway to carcinogenesis — and thus produce cancer through an identical mechanism. Their effects are functionally indistinguishable.

Now the mathematical part

As the slide shows, (Slide 9) - Background Additivity, the cancer incidence I(d) will be a linear function of the dose rate $\frac{1}{4}$ at low dose rates provided that the slope (F¹(D_O)) is positive. They defend the assumption that the slope is positive by arguing that even if there were a threshold, it would be a threshold for each cell; there would be a

distribution of these and at least one of which would be below the critical value. Since cancer is believed to be of single cell origin, this one activated cell would initiate the cancer, $F^{1}(D_{0})$ would be positive and the probability of response would be linear at low doses. They conclude

"... in environments already containing appreciable amounts of carcinogenic processes, the effects of any slight addition to these processes
will be proportional to the amount added. ... its implications are that
much previous investigation of the form of the dose-response relationship
at infinitesimal doses is irrelevant to the interpretation of animal
studies for the formulation of social policy."

It's hard to know what to say in the face of such confidence - for which there is no experimental data at all. These excathedra pronouncements are not believed by everyone but they continue to haunt some people including some in the regulatory agencies. The implications are, if this is true, that dose-response curves become approximately linear just below the observable range - so long as they are roughly linear in the observable range. Not everyone believes this - I certainly don't. Alice Whittemore, Mel Andersen and other pharmacokineticists still believe that tumor probabilities are proportional to effective doses and these generate very non-linear dose-response curves. And I suppose that the folks in Kurt Harris's lab at NCI still feel they have accomplished something by finding mutations in p53, a putative tumor suppressor gene in human hepatocellular carcinomas in China, despite the theory that says

these mutations are expected to be produced by "background carcinogens," not just aflatoxin.

MTD

The use of MTDs (Maximum Tolerated Doses) had been challenged throughout the period. Perry Gehring and Phil Watanabe had shown in 1976 that large doses could exceed metabolic and physiological thresholds, leading to prolonged retention in the body, formation of different metabolites and in some cases disproportionate increases in reactions between reactive electrophilic metabolites and macromolecules. They concluded that dose-dependent alterations in the fate of chemicals must be considered or at high doses you risk the likelihood of disproportionate increases in toxicity including carcinogenesis. They reported evidence of possible dose-dependent effects in styrene, ethylene glycol, aniline, carbon disulfide, 2-naphthylamine, benzopyrene, bis-hydroxycoumarin, salicyl-amide, amphetamine and sulfobromophthalin (Gehring, et al) (1976).

By the late 1970's, enough bioassay data had accumulated largely owing to NCT and later NTP studies, to provide a sufficient basis to examine the results of the studies for correlations between the responses in rats and mice. In 1979, Crouch and Wilson examined the carcinogenic potencies for 70 chemicals in the two species. They demonstrated empirically that good correlations existed for the potencies between the different species. This was an important finding, because if there were good interspecies correlations between potency estimates for rats and mice, then it was reasonable to believe that humans and animals might also be similar in their carcinogenic responses. But in 1985, Berstein, et al, reported

that the MTD's used in 186 NCI experiments were also highly correlated with potency.

(Slide 10) - MTD - Potency Correlation.

Correlations between MTDs in rats and mice are not surprising because both species could respond similarly to high doses of different chemicals. However, the strong correlation between these MTDs and the derived carcinogenic potencies is startling. The correlation is surprising because MTDs are determined in a 90 day study and this time period has been regarded as too small a fraction of a rodent's lifetime to reflect the presence of a carcinogenic process — much less predict the strength of the carcinogen. Berstein and co-workers showed (Slide 11) that potency estimates from NCI Bioassays were restricted to an approximately 30-fold range surrounding $\frac{\ln(2)}{TD_{EO}}$. The $\frac{TD}{50}$ is

virtually the same as the MTD. They used a one-hit model to show this and an idealized 2-Group experimental design, but they and others have shown that this high correlation is not sensitive to "reasonable" departures from either the experimental design or the extrapolation model used.

Rieth and Starr (1989), and others since, have investigated these correlations in detail. It's clear now that:

The correlations between the MTDs and the estimated potencies are real. They do not depend on a "selected" data base.

- The correlation in the carcinogenic potency estimates in both rats and mice are determined nearly entirely by the magnitude of the MTD used and only minimally by the extent of the carcinogenic response.
- e Based on upper limits, inferred potencies from some substances giving no response in the MTD-bioassay appear to pose a possible carcinogen risk as high as 10,000 times greater than other demonstrated carcinogens.
- o There is no reason to believe that the inverse MTD or its equivalent $1/TD_{50}$ should be regarded as a valid indicator of the low dose risk either to animals or to humans.

(Slide 12) - Starr's Comparison of 1/MTD with Potency Estimates of 83 Rat Carcinogens

There is a plausible explanation for the strong 1/MTD vs. potency correlation despite the fact that it is hard to prove. Many believe, as I do, that the high doses used in the bioassays are capable of producing carcinogenic responses not necessarily present at lower doses of the same chemical. Depending on the chemical the mechanisms will vary, e.g., altered metabolic pathways, ala Perry Gehring; altered physiology, e.g., d-limonene, NTA, saccharin, enhanced cell proliferation, ala Bruce Ames; altered endocrine or hormonal status, e.g., mammary and thyroid cancers and many others. If this is true, and more evidence is accumulating that it is, then high-to-low-dose extrapolation of carcinogenic effects, on

the basis of bioassay results only, is not credible. This is not to say that all high dose carcinogens are not carcinogenic at low doses. But the current NTP cancer bioassay data base with approximately 50% of the compounds testing positive contains many compounds that are probably not carcinogenic at low doses mixed in with many that are. The point is the test does not discriminate between them.

Back to Druckrey

While Secretary Fleming was reading the MIDER Report to Congress in 1960, Hans Druckrey in Germany was preparing to publish a review of his life-long work on chemical carcinogenesis. He published it in 1966 in a review article entitled:

"Quantitative Aspects in Chemical Carcinogenesis."

He and his colleagues were very well recognized - Druckrey, Preusman, Schmahl, Nakayima and others were major contributors to the field of chemical carcinogenesis. Their work spanned 25 years and included the testing of over 100 different chemical compounds in some 10,000 rats.

An example of his work on diethylnitrosamine is shown on the next slide. He administered daily doses in the drinking water until 50% of the animals in each group had liver tumors. The slide (Slide 13) shows that at the lowest daily dose rate (0.075 mg/kg/d) the cumulative dose required to produce cancer in 50% of the animals was only 1/15 of that required at a daily dose of 14.2 mg/kg/d.

This fact, that lower doses applied for a longer period could be more potent than larger doses of less duration was avidly learned and made a permanent feature of the lore of chemical carcinogenesis. But part of Druckrey's work seems to have been ignored. First, the price that is paid for a more efficient dose response is a longer induction time. And second, the cumulative doses involved are large, comparable to ingesting 1/10 of the MTD daily for a lifetime. This nitrosamine work was published in 1963 and, before that in 1961, Shubik had shown that not only were tumors generally slower developing at low doses, they also were more benign.

The Druckrey data are plotted in the next slide (Slide 14). You can see the increase in the induction time with decreasing dosage. The data show very clearly that 0.075 mg/kg/d is close to a practical threshold based on the fact that the induction time required for the development of the tumors approaches the lifetime of the animals. Druckrey's rats didn't live much longer than $2\frac{1}{2}$ years or \approx 900 days -- and these days they don't live nearly as long. And he concluded that

"With very low dosage the induction time can be longer than the life expectancy and that this is apparently a limiting factor in carcinogenesis."

He even had some regulatory advice for us:

"As a basis for future discussions it is proposed, that I per cent of the lowest dosage, which, given daily over the whole life span to susceptible experimental animals, produces cancer only at the end of

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the life span, can be considered as the maximum tolerable dose for human beings. This, however, only in such cases, in which a complete exclusion from [the] human is not feasible."

Some Conclusions

I don't have the answers to these current scientific issues in risk assessment, but I do have some suggestions as to how we should behave about them.

CANCER IS A VITAL HEALTH ISSUE - (Slide 15) - AND WE SHOULD TREAT IT SERIOUSLY AND DETERMINE WHERE THE REAL RISKS ARE.

- Face up to the fact that, as we use Quantitative Risk Assessment today, it is justified almost entirely as a very prudent regulatory standard if that's what we really want. It does not estimate risk and we will have to expect that it won't for decades.
- Stop the codification of risk assessment "acceptable levels" and risk assessment methodology in Federal Statutes. We are just creating other kinds of Delaney Clauses.
- Try harder to examine some of the cancer mythology that underlies our beliefs concerning thresholds, additivity and standard testing procedures for carcinogens.

- o Try to discourage media hype. Incessant coverage of the risk of real or suspect carcinogens buoyed up by the exaggerated claims of QRA determined risks makes it unnecessarily difficult to get the public to appreciate the overwhelming importance of smoking and the diet to cancer causation.
- Try to discourage the use of health warnings on trivial risks.

 It was absolutely appalling that for many years the health warning on saccharin in the U.S. was at least as strong as that on cigarettes. THAT'S NOT RISK COMMUNICATION! Cigarettes probably contribute some 150,000 deaths from cancer each year. Saccharin was banned by the FDA in 1977 on the grounds that it wasn't shown to be safe and on the Delaney Clause not because it was known to produce cancer in humans.
- o Finally, do some good research mechanistic work on cancer.

 There are, I think, three areas to focus on:
 - 1) Theoretical work
 - 2) Work at the cellular level, biochemistry, oncogenes
 - 3) Work in whole animals (not MTD Testing)
 - i. dosing regimens, effects of diet
 - ii. effective dose studies and pkBP

- iii. mechanism studies in vivo, e.g., foci development
- iv. secondary mechanism for non-mutagenic carcinogens

BASIC SCIENTIFIC ISSUES IN CANCER PISK ASSESSMENT

- ____ SIZE OF HUMAN CANLER RISK FROM LOW DOSE EXPOSURES
- · ___ RELIABILITY OF ANIMAL TO MAN EXTRAPOLATION
- ____ EXISTANCE OF DOSE-RESPONSE FOR CARCINOGENS
- ___ GRADABLE POTENLIES FOR CARLINGGENS
- . INSENSITIVITY OF ANIMAL STUDIES
- EXISTANCE AND MEASURABILITY OF THRESHOLDS
- · ___ INTERPRETATION OF NEGATIVE ANIMAL STUDIES
- · ---- HIGH TO LOW DOSE EXTRAPOLATION
- . INDEPENDENCE OR ADDITIVITY OF BACKGROUND

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A Continuation of The Journal of Cancer Research

VOLUME XVII

FEBRUARY, 1933

Number 2

SUGGESTED METHODS FOR THE STANDARDISATION OF THE CARCINOGENIC ACTIVITY OF DIFFERENT AGENTS FOR THE SKIN OF MICE

C. C. TWORT AND J. M. TWORT

(From the Laboratories of the Manchester Committee on Cancer)

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RELATIVE POTENCY OF CARCINOGENIC COMPOUNDS

TABLE I: Carcinogenic Compounds Arranged in Descending Order of Polency

| Compound | | No. of tu- mours | Per- cent- age of tu- mours (A) | Papil- Ioma | Epi- theli- oma | Average latent period (B) | Index (A/B×100) |
|--|----|------------------------|---|----------------|-----------------------|---------------------------|--------------------|
| 1. 9:10-Dimethyl-1:2-benzanthracene | | 13 | 65 | 6 | 7 | 43 | 151 |
| 2. Methylcholanthrene (a) | | 18 | 100 | 1 | 17 | 99 | 101 |
| 3. Methylcholanthrene (b) | 8 | 5 | 62.5 | 0 | 5 | 151 | 41 |
| 4. Methylcholanthrene (a and b added to- | | | | | | | 7. |
| gether) | | 2.3 | 88.5 | 1 | 22 | 109 | 80 |
| 5. 3:4-Benzpyrene (from pitch) | | 10 | 100 | 2 | 8 | 127 | 79 |
| 6. 3:4-Benzpyrene (synthetic) | | 7 | 78 | 2 | 5 | 109 | 72 |
| 7. 3:4-Benzpyrene (5 and 6 added to- | | | ! | | | | ' - |
| gether) | 19 | 17 | 89.5 | 1 | 13 | 119 | 75 |
| 8. Cholanthrene | 49 | 28 | 57 | 5 | 2.3 | 112 | 51 |
| 9. 5:6-cycloPenteno-1:2-benzanthracene | 14 | 13 | 93 | 1 | 12 | 194 | 48 |
| 10. 2-Methyl-3: 4-benzphenanthrene | | 12 | 75 | 5 | 7 | 155 | 48 |
| 11. 10-Methyl-1: 2-benzanthracene | | 12 | 66.5 | 2 | 10 | 147 | 45 |
| 12. 5:6-Dimethyl-1:2-benzanthracene | | 16 | 84 | 0 | 16 | 220 | 38 |
| 13. 6-isol'ropyl-1: 2-benzanthracene | | 11 | 73.5 | 1 | 10 | 204 | 36 |
| 14. 3:4:5:6-Dibenzcarbazole | | 9 | 47.5 | 4 | 5 | 143 | 33 |
| 15. 3:4:8:9-Dibenzpyrene | | 10 | 59 | 0 | 10 | 205 | 29 |
| 16. 5-Methyl-1: 2-benzanthracene | | 7 | 87.5 | 2 | 5 | 317 | 28 |
| 17. 5-Ethyl-1: 2-benzanthracene | | 7 | 77.5 | 2 | 5 | 285 | 27 |
| 18. 1:2:5:6-Dibenzanthracene | | 41 | 6.3 | 8 | 33 | 239 | 26 |
| 19. 3:4-Benzphenanthrene | 18 | 12 | 67 | 5 | 7 | 387 | 17 |
| 20. 1:2:5:6-Dibenzcarbazole | | 4 | 44.5 | 1 | 3 | 263 | 17 |
| 21. 5-n-Propyl-1: 2-benzanthracene | | 6 | 30 | 3 | - 3 | 192 | 16 |
| 22. 3: 4:5:6-Dibenzacridine | | 11 | 39.3 | 2 | 9 | 357 | 1 11 |
| 23. 3'-Methyl-1:2:5:6-dibenzanthracene | | 7 | 28 | 1 | 6 | 325 | 9 |
| 24. 1:2:5:6-Dibenzacridine | 25 | 6 | 24 | 2 | 4 | 350 | 7 |
| Тотм. | | 305 | | 60 | 245 | | * |

is still the possibility of an error due to the fact that a number of animals may die soon after the first tumours are seen and before the majority have appeared Theoretically it would be an advantage in obtaining a quantitative comparison of the potency of several compounds if all the experiments were carried out on pure-line mice under as nearly as possible the same conditions. This would reduce the variation between the batches of animals used for different compounds, but the results of the comparison would then apply only to that

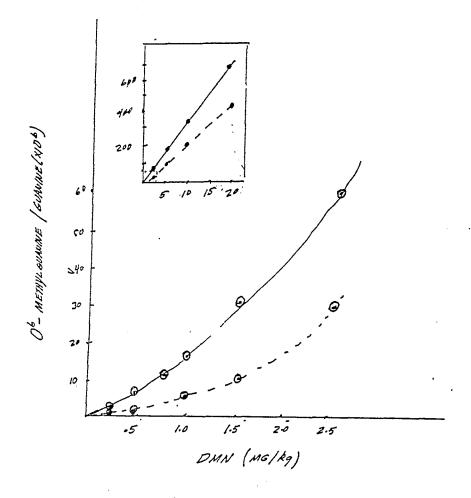
Table 2
Occupational Cancers

FROM DOLL (1977) URIGINS OF HUMAN CANCER COLD SPRING HARBOR VOL 4

| Agent | Occupation | Site of cancer | | | |
|---------------------------------------|---|---------------------------------|--|--|--|
| Ionizing radiations | ; · | | | | |
| radon | certain underground miners (uranium, fluorspar, hematite) | bronchus | | | |
| X rays, radium | radiologists, radiographers | skin . | | | |
| radium | luminous dial painters | bone | | | |
| Ultraviolet light | farmers, sailors | skin | | | |
| Polycyclic hydrocarbons in | chimney sweeper's | scrotum | | | |
| soot, tar, oil | manufacturers of coal gas | skin | | | |
| | many other groups of exposed industrial workers | bronchus | | | |
| 2-Naphthylamine; 1-naph- thylamine | chemical workers; rubber workers; manufacturers of coal gas | bladder | | | |
| Benzidine; 4-aminobiphenyl | chemical workers | bladder | | | |
| Asbestos | asbestos workers; shipyard and insulation workers | bronchus pleura and peritoneum | | | |
| Arsenic | sheep dip manufacturers; gold miners; some vine- | skin and bronchus | | | |
| (| yard workers and ore smelters | | | | |
| Bis (chloromethyl) ether | makers of ion-exchange resins | bronchus | | | |
| Benzene | workers with glues, varnishes, etc. | marrow (leukemia) | | | |
| Mustard gas | poison gas makers | bronchus; larynx; nasal sinuses | | | |
| Vinyl chloride | PVC manufacturers | liver (angiosarcoma) | | | |
| (Chrome ores) | chromate manufacturers | bronchus | | | |
| (Nickel ore) | nickel refiners | bronchus; nasal sinuses | | | |
| (Isopropyl oil) | isopropylene manufacturers | nasal sinuses | | | |
| * | hardwood furniture makers | nasal sinuses | | | |
| * | leather workers | nasal sinuses | | | |

^{*} Specific agent not identified.

06-METHYLGUANNE LEVELS IN RAT LIVER DNA
AFTER IP ADMINISTRATION OF SINGLE DOSES OF DMN
PEgg (1978)



Mantel and Bryan's Interpretation of Negative Studies

$$0 - (1-P)^{100} = (100-99\%) = 0.01$$

$$1-p = 0.955$$

o _ Probet corresponding to
$$10^{-8} = -0.612$$

$$o - Upper limit on the 1/5/2 = 3.305-(-0.6/2)$$

= 3.917

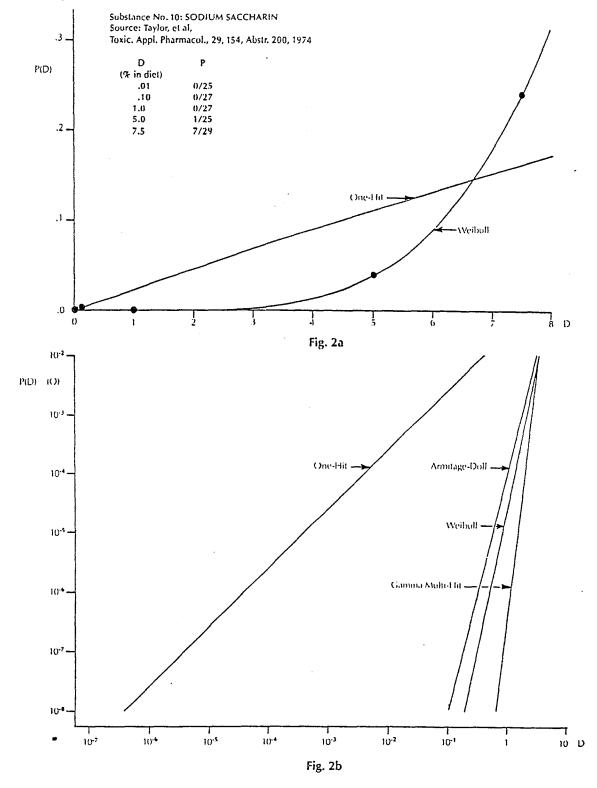
TABLE 4
ESTIMATED VIRTUAL SAFE DOSE (VSD) FOR FOUR MODELS FOR FOURTEEN SUBSTANCES

| Estimated VSD at Risk Level 10-6 | | | | |
|----------------------------------|------------------------|----------------------|-----------------------|--|
| One-Hit | Armitage-Do | oll Weibull | Multi-Hit | |
| 2.0×10^{-5} | 1.9 x 10-4 | .52 | .80 | |
| 3.4×10^{-5} | 7.9 x 10 ⁻⁴ | 4.0×10^{-2} | .28 | |
| 4.5 x 10 ⁻⁵ | .35 | .59 | 2.3 | |
| 5.2×10^{-6} | 1.6×10^{-3} | 1.7×10^{-3} | 3.8×10^{-3} | |
| 3.2×10^{-5} | 1.9×10^{-2} | 1.9×10^{-2} | 7.7×10^{-2} | |
| 2.0×10^{-2} | 2.0×10^{-2} | 2.1×10^{-9} | 3.9×10^{-10} | |
| 2.1×10^{-4} | 2.2×10^{-4} | 2.6×10^{-4} | 2.6×10^{-4} | |
| 8.4×10^{-8} | 4.2×10^{-3} | 4.3×10^{-3} | 1.3×10^{-2} | |
| 1.6×10^{-4} | 4.0×10^{-4} | 3.1×10^{-2} | 3.7×10^{-2} | |

SOCIUM SALLHARIN

| | 4.3 x 10 ⁻⁵ | .33 | .53 | 1.1 |
|---|------------------------|------------------------|----------------------|------------------------|
| • | 5.5 x 10-4 | 4.5 | 6.0 | 33.5 |
| | 5.7×10^{-6} | 2.2×10^{-5} | 1.2×10^{-3} | 6.7×10^{-3} |
| | 2.8×10^{-4} | 6.4 x 10-4 | 1.7×10^{-2} | 4.9 x 10 ⁻² |
| | 3.7×10^{-5} | 5.7 x 10 ⁻⁵ | 1.1×10^{-3} | 3.8 x 10 ⁻³ |

FROM FOOD SAFETY COONCIL PEPORT TUNE 1980 0 P 149



BALKGROUND ADDITIVITY AT LOW DOSES CRUMP, HOEL & PETO (1977)

- I, = INCIDENCE RATE DUE TO BACKBROUND CARRINGGENS
 INDEPENDENT OF PRIMARY CARCINOGEN
- I = INCIDENCE RATE DUE TO BACKGROUND CARCINGENS
 THAT ACT WITH MECHANISMS IN COMMON WITH THE
 PRIMARY CARLINGEN

$$I(d) = I_1 + I_2$$

= $I_1 + F(d'+\cdots+d'''+\beta d) = I_1 + F(D_0+\beta d)$

AT LOW DOSES:

AS LONG AS F'(Do) IS POSITIVE, I'(d) WILL BE PROPORTIONAL to d FOR LOW DOSES

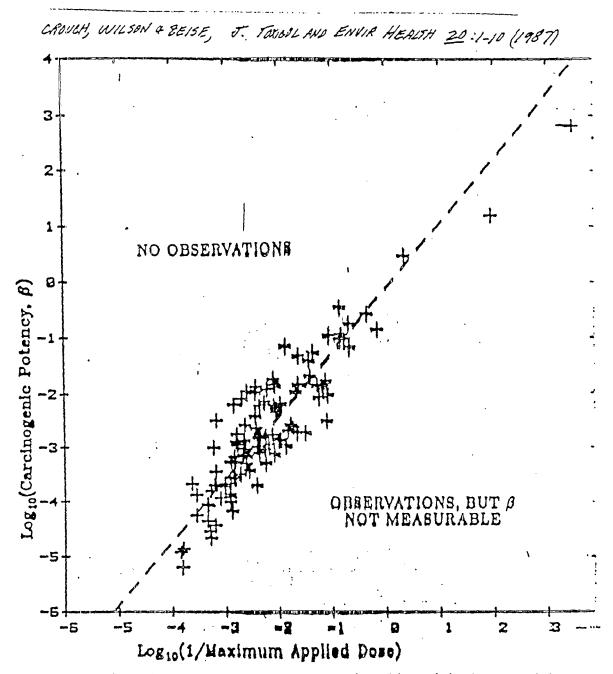


FIGURE 1. Logarithm of carcinogenic potency versus logarithm of the inverse of the applied dose for female B6C3F1 mice in the NCI/NTP series of bloassays. Each point repeats separate experiment. The dotted line is a least-squares fit to these points.

BERNSTEIN ET. AL. (1985)

$$R(d) = 1 - e^{-\beta d}$$

$$\beta = -\frac{1}{2} \ln(1 - R_d)$$

$$\ln \beta = \ln(\frac{1}{2}) + \ln[-\ln(1 - R_d)]$$

$$At THE TO_{50} \cdot \cdots \cdot R_0 = \frac{1}{2}$$

$$\ln \beta = \ln(\frac{1}{TO_{50}}) + \ln(\ln 2)$$

$$\beta = \frac{\ln 2}{TO_{50}}$$

PEq. Toxicol o PHARMICOL 10, 160-73 (1989) RIETH AND STARR

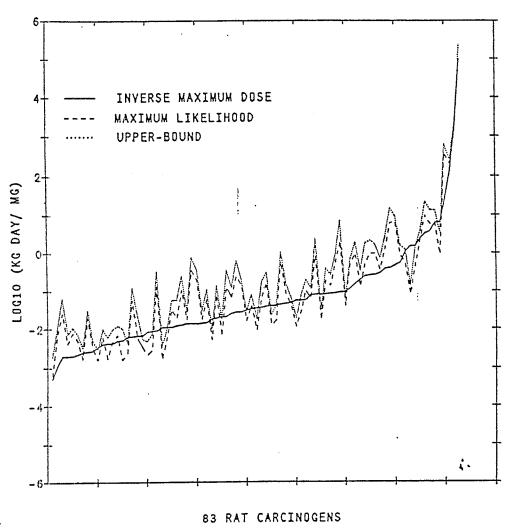


Fig. 4. Comparison of the inverse of the maximum dose tested with maximum likelihood and upper-bound potency estimates of rat carcinogens.

| Druckey | et el, 1963 |
|---------|-------------|
| (/ | |

| d daily dasagl mg/kg | Final Casunoma yild puportins | doc | induction time |
|-------------------------------|--|------|-------------------|
| 14.2 | 5/5 | 1000 | 68 |
| 9.6 | 25/25 | 963 | 101 |
| 4.8 | 25/25 | 660 | 137 |
| 2.4 | 34/34 | 460 | 192 |
| 1.2 | 36/36 | 285 | 238 |
| 0.6 | 49/49 | 213 | 355 |
| 0.3 | 67/67 | 137 | 457 |
| 0.15 | 27/30 | 91 | 609 |
| 0.075 | 5/7 | 6# | 840 |
| 1:200 | | 1:15 | 1:12 |

 $dt^{m-1} = k$ $dt = \frac{k}{m-1}$

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| O DEATHS | 475,000 900,000 |
|---------------------|--------------------|
| O HEALTH CARE | \$ 22 Billion |
| O LOST PRODUCTIVITY | _ # 9 |
| NORTALITY | 4 |
| | \$ 72 BILLION |

The Surgen General' Report on Nutrotion a Health (1988)
DHHS (PHS) Publication No 88-50210

REFERENCES

- (1) Doll, R., Introduction in Origins of Human Cancer, Book A, Incidence of Cancer in Humans. Cold Spring Harbor Conferences on Cell Proliferation, Vol. 4 (1977) Edited by Hiatt, H.H., Watson, J.D. and Winsten, J.A.
- (2) Doll, R., Vessey, et al. The Mortality of gas-workers. Final report of a prospective study. Br.J.Ind.Med. 29, 394 (1972).
- (3) Pegg, Anthony E., Alkylation of Rat Liver DNA by Dimethylnitrosamine: Effect of Dosage on 0⁶-Methylguanine, J. Nat'l Cancer
 Inst., 58, No. 3 (1977) 681-7.
 - (4) Pegg, A.E., and Georgiani Hui, Formation and Subsequent Removal of 0⁶-methylguanine from DNA in Rat Liver and kidney after small doses of DMN. Biochem. J. <u>173</u>, 739-748 (1978).
 - (5) Mantel, N. and Bryan, W.R., "Safety" Testing of Carcinogenic Agents,
 J. Nat'l Can. Inst. 27, No. 2, 455-49 (1961).
 - (6) Weil, C. Statistics vs. Safety Factors and Scientific Judgment in the Evaluation of Safety for Man, <u>Toxicol. and Applied Pharmacol.</u> 21, 454-463 (1972).

- (7) Hearings before the Committee on Interstate and Foreign Commerce,
 House of Representatives, 86th Cong., 2d Sess. (1960).
- (8) Gehring, P.J., Blau, G.E., Wantanabel, P.G., Pharmacokinetic studies in evaluation of the toxicological and environmental hazard of chemicals. In Adv. in Modern Toxicology New Concepts in Safety Evaluation, Hemisphere Publishing, Wash., D.C. (1976).

Introduction to Background Materials

Moeller

Cole

TOOLS OF RISK ANALYSIS

Applications of Epidemiology

- I. Overview
- II. Risk assessment epidemiology
 - A. Definition: a description of the change in the

incidence rate of a disease due to a known change in the level of

exposure to a cause

- B. Purposes: guide public health policies
 - guide the regulatory process

assist in tort resolution

C. Foundations: - basic science - Nature of affect

- animal studies describe potency

D. Growing importance of epidemiology: - would the workest + most advances in methodology difficult. - but most reduced reliance on animal

extrapolation is objective reduced reliance on animal research (species bookies)

generalization - Subjective - bases in law (opposition to the use of animal) animals have a single exposure and the desire to produce an affect

III. Epidemiology - general

A. Definitions: the study of the distribution and determinants of disease in man

an observational science dealing with the environmental causes of

diseases of human beings

- B. Strengths human beings
 - human lifestyles
- C. Limitations non-experimental
 - often qualitative
- IV. Selected measures
 - A. Incidence rate

I = new cases/(population x time)

example: the incidence rate of leukemia is 10.1 cases per 100,000 person-years

B. Risk

R = new cases/population

example: the lifetime risk of developing

leukemia is 700 per 100,000

persons, or 0.7%

C. Relative incidence rate (relative risk, RR) R# = the incidence rate in an exposed group divided by that in a non-exposed group example: the RI of leukemia among rubber

Standardized mortality ratio effects of age shave been eliminated SMR = the number of death. in an occupational group) divided by the number of deaths expected among pliofilm workers the SMR example: is 337 (base = 100)

V. Study designs - general

- Descriptive studies as the individual human being is not studied - a group is study correlational officies

 Follow-up (cohort) studies analytic:

 a. prospective - limit the future individual is dollared.

 b. retrospective - past most common
- Case-control les important For RA selection of disease boain with people with and without disease & determine expasure
- Proportional mortality ratio (PMR)

Study designs - specific VI.

Example:

The retrospective follow-up design

1165 rubber hydrochloride (pliofilm) workers followed-up from 1950-81 experienced 9 deaths from leukemia with 2.7

expected, an SMR of 337

fast, inexpensive / - 2 years Advantages:

exposure based

profile of effects (all causes of death) relatively free of bias (systamatic error)

inadequate exposure-possible (info terrible) Limitations:

inadequate exposure documentation -

usual

prone to chance -

prone to confounding afternative cause

The case-control design not often used for RA contsidered not very precise

Example:

138 adults with leukemia, resident in Olmsted County MN, were compared with 276 adults without leukemia. Information on benzene exposure was abstracted from medical records. Among persons with benzene exposure, the RI of leukemia was 3.3 compared to persons without

exposure.

Advantages:

fast 6 months profile of exposures control confounding

precise (not prone to chance) suitable for rare disease

Limitations:

single disease

only relative measures of disease prone to bias - difficult to prove the controls

are truly the same as the cases Interpretations - How do these influence outcome VII.

Chance - make study large

Bias - try to deal with possible biases in design phase lots of data on other Known В.

diseases Valid D.

causal null

Comment:

not mutually exclusive

not permanent

Causality VIII.

Individual study strength internal consistency biological credibility

Abstract, general case external consistency response to manipulation

ě

IX. Benzene and leukemia - A model risk assessment

- Basic science not genotoxic - not a mutagenic damages chromosomes - not clear by what mechanism
- В. Animal studies carcinogenic leukemogenicity problematic 14 pas
- 17 studies 7 2 neg all studies were poor quantification of exposure Epidemiologic studies on exposus some potential confounding - other solverts
 - Epidemiologic data*
 - observed deaths: Joukemen
 - 9.6 - expected deaths: - total deaths: 1273
 - mean cum. exposure: 42 ppm-yrs intesty level x years
 - Risk assessment

30

- 19-9.6 = 9.4- excess deaths:
- 9.4/1.273 = 7.4/1000 ~ thout - excess deaths/1000:
- 7/1000 - baseline risk:
- doubling dose:

(14/14.7)(42 ppm-yrs) = 40 ppm-yrs

- how much does he need to be exposed to double the risk Х. The OSHA standard 20ppm for 2 urs
 - For many years Α. = 10 ppm 8 hr TWA 30 yrs x 10 ppm = 300 ppm-yrs \sim 7 doublings = 800/1000 = unacceptable ~7 additions ~ 56 deaths/1000
- Currently = 1 ppm 8 hr TWA 30 ppm yrs ≥ 1.75 baseline ≥ 5 excess deaths/1000 exposed

- C. Issues Model assumes -
 - linear dose response
 - non-threshold
 - other

4 September 1991 Philip Cole, M.D.

Austin H, Delzell E, Cole P: Benzene and leukemia: A review of the literature and a risk assessment. Am J Epidemiol 127:419-439, 1988. APPLIED OCCUPATIONAL AND ENVIRONMENTAL HYGIENE, Vol. 5, No. 7. pages 453 - 463 (July 1990).

Notice of Intended Changes-Benzene

Editor's Note: In anticipation of significant interest and to ensure reader awareness of the proposed revision of the Threshold Limit Value (TLV) for benzene, publication of this revised documentation is issued at this time and in advance of the publication of the Threshold Limit Values and Biological Exposure Indices for 1990–1991 booklet. The recommendation of the Chemical Substances TLV Committee received approval from the ACGIH Board of Directors and members in attendance at the annual ACGIH business meeting on May 16, 1990. The recommendation is that benzene be listed on the Chemical Substances TLV Notice of Intended Changes for 1990–91 at 0.1 ppm as a time-weighted average (TWA) with a Skin notation and designation as an A1 carcinogen (confirmed human carcinogen).

This proposed reduction for the adopted benzene TLV-TWA of 10 ppm and A2 carcinogen designation (suspected human carcinogen) will undoubtedly prompt speculation as to the basis for the proposed revision. An estimated exposure to benzene of 238,000 U.S. workers and usage of more than 11 billion gallons of benzene per year are added incentives to publish the revised documentation at this time. The proposed revision will remain on the Notice of Intended Changes for a period of at least two years during which comment and substantive evidence for or against the appropriateness of the revised TLV is solicited by the TLV Committee.

This publication of the documentation in *Applied* provides an additional opportunity for comment.

Benzene

CAS: 71-43-2

Benzol; phenyl hydride; cyclohexatriene; coal naptha

C₆H₆ Skin

TLV-TWA, 0.1 ppm (0.3 mg/m³) A1—Confirmed Human Carcinogen

TLV-TWA, 100 ppm, 1946 TLV-TWA, 50 ppm, 1947

TLV-TWA, 35 ppm, 1948-1956

TLV-TWA, 25 ppm, 1957–1962

TLV-Ceiling, 25 ppm, Skin, 1963-1976

TLV-TWA, 10 ppm,A2, Skin, 1977-present; Skin notation deleted 1978

TLV-STEL, 25 ppm, A2, 1980-1987

TLV-TWA, 0.1 ppm, A1, Skin: proposed 1990

Documentation revised, 1990

Chemical and Physical Properties

Benzene is a colorless, highly flammable, nonpolar liquid with an odor that is characteristic of aromatic hydrocarbons. Benzene can be supplied as industrial grade, ni-

tration grade, or refined. Physicochemical properties of reagent grade benzene include:

Molecular weight: 78.11

Specific gravity: 0.87865 at 20°C

Melting point: 5.5°C Boiling point: 80.1°C

Vapor pressure: 75 torr at 20°C Closed cup flash point: -11.1°C Autoignition temperature: 562°C Flammability limit in air: 1.5-8.0 vol%

Odor threshold: 12 ppm

Saturated air at 25°C contains 120,000 ppm

Solubility: 0.180 g/100 ml water at 25°C; miscible in all proportions with carbon tetrachloride, ethanol, chloroform, diethyl ether, carbon disulfide, acetone, glacial acetic acid, and oils.

Major Uses and Sources of Occupational Exposure

At one time, benzene was an important solvent, especially for inks, rubber, lacquers, and paint removers. At present, such uses are minimal; most benzene is consumed in the chemical industry as a raw material for numerous organic chemicals and in plastics manufacture. It is found in gasoline from trace amounts to as much as 30 percent in some countries (U.S. average, 1–3%). Total benzene usage exceeds 11 billion gallons per year, (1) and it is estimated that 238,000 employees in U.S. petrochemical plants, petroleum refineries, coke and coal operations, tire manufacturers, bulk terminals and plants, and in truck transport are exposed to benzene. (2)

Benzene is a myelotoxicant, known to suppress bone marrow cell proliferation and to induce hematologic disorders in humans and in animals. Signs of benzene-induced aplastic anemia include suppression of leukocytes (leukopenia), red cells (anemia), platelets (thrombocytopenia), or all three cell types (pancytopenia). Classic symptoms include weakness, purpura, hemorrhage, pancytopenia, and aplastic anemia.

Animal Studies

Subchronic

When Sprague–Dawley rats and CD-1 mice of either sex were exposed by inhalation to benzene at 1, 10, 30, or 300 ppm, 6 hours per day, 5 days per week for 13 weeks, treatment-related pathology was observed in the high dose (300 ppm) groups of both species. (3) In mice, hematologic changes included decreased hematocrit, total hemoglobin, erythrocyte/leukocyte count, platelet count, and myeloid:erythroid ratio. In rats, decreased lymphocyte count and a relative increase in neutrophil count were the only exposure-related clinical change. Histopathological changes

were observed in the testes and ovaries at concentrations below 300 ppm, and lesions were observed in the thymus, bone marrow, lymph nodes, spleen, ovaries, and testes in mice inhaling 300 ppm. The alterations were more severe in the males than in the females. In rats, the only exposure-related pathology was a slight reduction in femoral marrow cellularity at 300 ppm.⁽³⁾

Studies to identify the target cells for benzene hematopoietic toxicity indicated that benzene exposure damaged mouse pluripotent stem cells, the colony-forming cell units in the spleen, and the progenitor cells for granulocytes and macrophages. (4-6) Hematopoietic depression in rodents was observed at benzene concentrations as low as 103 ppm after a 5-day exposure. (7) Cronkite et al. (8,9) reported a series of studies where CBA/CA mice were exposed to benzene at 10, 25, 100, 300, or 400 ppm, 6 hours per day, 5 days per week for 2, 4, 8, and 16 weeks. Exposure to 100 ppm or greater for two weeks reduced bone marrow cellularity. (8) When C57BL/6J mice inhaled 300 ppm benzene 6 hours per day, 5 days per week for a total of 115 exposures, the numbers of B-lymphocytes in bone marrow and spleen and the numbers of T-lymphocytes in thymus and spleen were reduced.(10) When BALB/C mice were exposed at 50 or 200 ppm benzene 6 hours per day for 7 or 14 days, the ratios and the absolute numbers of T- and B-lymphocytes in blood and spleen were depressed.(11) Depression of B-lymphocytes was dosedependent, and it was more severe than that of the T-cells.(11) When male C57BL mice inhaled 10 ppm, 6 hours per day for 6 days, a significant depression in colony-forming units in B-lymphocytes was observed; similar inhalation of 31 ppm resulted in depressed blastogenesis of T-lymphocytes. (12)

Chronic/Carcinogenicity

When groups of 40 CD-1 mice were exposed to benzene in air at 100 or 300 ppm, 6 hours per day, 5 days per week for life, two mice in the high dose group developed myelogenous leukemia. No leukemia was observed in the 100-ppm dose group. (13) Snyder et al. (14) found that after groups of 40 C57BL mice inhaled 300 ppm benzene for 6 hours per day, 5 days per week for 2 years, eight cases of lymphoreticular neoplasia (six thymic lymphocytic lymphomas, one plasmocytoma, and one hemocytoblastic leukemia) occurred; two mice in the control group developed lymphocytic lymphomas. The incidence of tumors in the benzene-treated mice was significantly greater (p = 0.005) than that in the control.(14) In a lifetime carcinogenicity bioassav in which oral doses of benzene were administered at 50 and 250 mg/kg-day, 4-5 days per week for 52 weeks, there was a dose-dependent increase in total cancers.(15) The most prominent rat tumors observed were Zymbal gland carcinomas, mammary carcinomas, and leukemia. When Wistar rats and Swiss mice were given benzene at 500 mg/kg-day, 4 or 5 days per week for 104 or 78 weeks, respectively, the numbers of Zymbal gland carcinomas, hemolymphoreticular neoplasias, and total malignant tumors were increased in the rats; increases in mouse Zymbal gland dysplasia and carcinomas, mammary carcinomas, pulmonary tumors, and total malignant tumors were observed. (16)

In the National Toxicology Program lifetime bioassay, (17) 50 F344/N rats of each sex per dose group were treated with benzene by oral gavage at doses of 50, 100, or 200 mg/kg-day for the males and at 25, 50, or 100 mg/kg-day for the females for two years. Similar groups of B6C3F1 mice of both sexes were treated with 25, 50, or 100 mg/kgday. For the male and female rats, increases of Zymbal gland carcinoma, squamous cell papilloma, and squamous cell carcinoma of the mouth were observed. In the male rats, squamous papilloma and squamous cell carcinoma of the skin were also increased. For male mice, increased numbers of animals with Zymbal gland carcinoma, malignant lymphoma, alveolar/bronchiolar carcinoma, and alveolarbronchiolar adenoma or carcinoma (combined), Harderian gland adenoma, and squamous carcinoma of the preputial gland were observed. For female mice, increased numbers of animals compared to the control were afflicted with malignant lymphoma, ovarian granular cell carcinoma, carcinosarcoma of the mammary gland. alveolar/bronchiolar adenoma, and alveolar/bronchiolar carcinoma were reported.(17)

Cronkite⁽¹⁸⁾ conducted a carcinogenicity bioassay wherein male and female C57BL/6 and CBA/Ca mice inhaled 100–300 ppm benzene, 6 hours per day, 5 days per week for 16 weeks and found benzene-induced leukemia in the males. When mice inhaled 25 ppm benzene for as few as ten such exposures, lymphopenia resulted.⁽¹⁸⁾

Reproductive/Developmental

Studies on the potential developmental toxicity of benzene administered by subcutaneous injections, ingestion, or inhalation have generally failed to show significant adverse effects in mice, rats, or rabbits (for review, see Schwetz⁽¹⁹⁾). Adverse developmental effects have been described in an unpublished rat bioassay performed by Litton Bionetics⁽²⁰⁾ wherein Sprague–Dawley rats inhaled 10–40 ppm benzene, 6 hours per day on days 6–15 of gestation. Embryonic death increased from the control (6.2%) to 8.1 and 9.5 percent for rats exposed to 10 and 40 ppm benzene, respectively. However, the Litton study⁽²⁰⁾ was confounded by the high ambient temperature in one of the exposure chambers during the study; maternal hyperthermia is a known rodent teratogen.

Kuna and Kapp⁽²¹⁾ conducted an inhalation study in which pregnant Sprague–Dawley rats were exposed to benzene at 10, 50, or 500 ppm 7 hours per day on days 6–15 of gestation. Significant reductions in mean maternal body weight gain occurred. Mean fetal body weight was reduced. Fetal crown–rump distance was decreased significantly at 500 ppm, and developmental delay was evident upon examination of the fetal skeletons. Benzene was judged by these authors⁽²¹⁾ to be fetotoxic in rats at 50 and 500 ppm and to manifest teratogenicity at 500 ppm. Coate *et al.*⁽²²⁾ found that when pregnant Sprague–Dawley rats inhaled 1, 10, 40, or 100 ppm benzene 6 hours per day on days 6–15 of gestation, no maternal toxicity was noted; however,

a reduction in mean fetal body weight at 100 ppm was observed. No teratogenic effects were found.(22) When pregnant Swiss-Webster mice were exposed to 5, 10, or 20 ppm benzene in air on days 6-15 of gestation for 6 hours per day, alterations in the numbers of hematopoietic colony-forming cells in the progeny were recorded.(23) Marked reductions in erythroid colony-forming cells were observed at all benzene concentrations studied, and inhalation of 10 or 20 ppm also decreased the numbers of granulocytic colony-forming cells. When mice, previously exposed in utero to 10 ppm benzene, were re-exposed to 10 ppm for 6 hours per day for 2 weeks, a marked reduction in the numbers of bone marrow differentiated ervthroid colony-forming cells occurred. (23) Keller and Snyder(23) interpreted these data as an indication that alterations of the murine hematopoietic system induced by neonatal benzene exposure could persist into adulthood.

Ungvary and Tatrai⁽²⁴⁾ exposed CFLP mice and NZ rabbits to benzene at 154 or 308 ppm, 24 hours per day, throughout days 6–15 of gestation. Benzene was detected in fetal blood and in amniotic fluid. At 308 ppm, retarded skeletal development and reduced fetal body weight were observed in mouse fetuses, and spontaneous abortions were reported in rabbits.⁽²⁴⁾

Genotoxicity Studies

Benzene exposure can cause chromosomal aberrations in animals and in humans. Benzene exposure induces clastogenesis, sister chromatid exchange, and micronuclei both *in vivo* and *in vitro*. Benzene exposure has been shown to induce aneuploidy in dividing cells, presumably through inhibition of tubulin assembly during mitosis. However, benzene exposure has failed consistently to induce point mutations in genotoxicity test systems.

Point Mutation

In the *Salmonella typhimurium* gene mutation assay, benzene proved consistently negative for mutagenesis in plate-incorporation assays with or without microsomal enzyme activation. (26–29) McCarroll *et al.* (30) published the only positive result using a microsuspension assay with hepatic microsomal activation such that an increase in the numbers of revertants in *Salmonella* strain TA100 was observed.

Benzene exposure inhibited the growth of DNA repair deficient *Escherichia coli* strain WP100 (uvra⁻, recA⁻, but no such effect was observed in repair proficient strains.⁽³¹⁾ Growth inhibition was also observed in DNA repair deficient *Bacillus subtilis* strain M45 (rec⁻)⁽³²⁾ but benzene was considered without mutagenic activity in the *E. coli* PolA assay, an indication that the DNA polymerase activity was not critical for repair of benzene-induced damage to nucleic acid.⁽³³⁾ Benzene was reported negative in *Saccharomyces cerevisiae* gene conversion and mitotic crossing-over assays;⁽³⁴⁾ however, it was considered mutagenic for *S. cerevisiae* strains D61-M and D6.⁽³⁵⁾

When benzene was fed to Drosophila melanogaster at

up to 2.5 percent in the diet, no evidence for a mutagenic response using the eye pigmentation as a genetic market was found. When *Drosophila* were placed in air containing 27,000 ppm for 60 minutes (20% survival), a significant increase in spermatogonial crossing-over was observed and mutation frequency and translocation frequency were increased. These data were considered indicative of the stage-specific nature of benzene-induced spermatogonial mutagenesis in *Drosophila*. Benzene exposure altered gene expression as measured in the *Drosophila* wing morphology assay, but results using the *Drosophila* eye spot assay were judged negative. or at most equivocal. In grasshopper embryos, benzene exposure was associated with mitotic arrest, multipolar division, and chromosome lags.

Benzene was tested in a colloborative study of 12 laboratories using a variety of cell lines and genetic markers. (42) Benzene was mutagenic without hepatic enzyme (S9) activation in the mouse lymphoma L5178Y (TK+/+) assay in one laboratory, it was mutagenic in the Chinese hamster V79 cell assay at the oubain-resistant locus (NaK-ATPase defective) in one laboratory, and it was mutagenic at the 6-thioguanine resistance locus (HGPRT-) in one laboratory. Mutagenic activity was observed with S9 activation in the mouse lymphoma L5178Y (TK+/+) assay for trifluorothymine resistance (TK-) in two of the laboratories, and mutagenicity was observed in the mouse lymphoma L5178Y (TK+/+) assay for oubain-resistance in one of the laboratories. Benzene was considered mutagenic without exogenous activation for 6-thioguanine resistance in human AHH-1 lymphoblasts. Except for the human lymphoblast and Chinese hamster V79 studies (which were not repeated in other laboratories), the findings for benzene point mutation could not be confirmed by other laboratories involved in the collaborative study. (42) Therefore, potential point mutation associated with benzene exposure in cultured mammalian cells is considered inconclusive based on the studies published to date.

Chromosomal Aberration

Benzene treatment induces chromosomal structural changes and aneuploidy in cultured mammalian cells. In cultured human lymphocytes, chromosomal aberrations were observed after three hours of incubation with 9–88 µg benzene/ml with or without S9 activation. (43) Aberrations were also observed in Chinese hamster lung fibroblasts after treatment with 1100 µg benzene/ml and in Chinese hamster ovary (CHO) cells at 100 µg benzene/ml with S9 activation. Aneupoloidy was reported in Chinese hamster primary hepatocytes treated with benzene at 62.5 µg/ml. (44)

Benzene itself failed to induce sister chromatid exchange (SCE) in cultured human lymphocytes without exogenous metabolic activation (S9), but benzene metabolites increased SCE in a dose-dependent fashion. (45) The primary benzene metabolites (phenol, catechol, hydroquinone) are transformed to benzo(semi)quinones, which presumably act as the ultimate genotoxic agents. (45) Ca-

techol and hydroquinone were potent SCE inducers at $4.4\,\mu\text{g/ml.}^{(46)}$ Glutathione (GSH) inhibited benzene-induced SCE formation, and it was hypothesized that GSH conjugation to benzene metabolites prevented DNA damage. Benzene and its metabolites were reported to decrease mitotic index, to inhibit cell cycle transverse, and to increase GCE frequency in cultured human T-lymphocytes. The relative potency of benzene metabolites for SCE induction were catechol > 1,4-benzoquinone > hydroquinone > 1,2,4-benzenetriol > phenol > benzene. Benzene.

Tice *et al.*⁽⁴⁹⁾ found a concentration-dependent increase in DBA/2 mouse bone marrow lymphocytes after a single, 4-hour inhalation study of benzene at 28–3000 ppm; an increase in SCE was detected at 28 ppm. This response was strain-dependent as DBA/2 mice were more sensitive than C57BL/6 mice, young DBA/2 mice (three months) were more sensitive than older mice (10 months), and male mice were more sensitive than female mice. Following intraperitoneal injection, a linear dose-dependent increase in SCE was observed in DBA/2 mice.⁽⁴⁹⁾

DIVA Damage

Benzene failed repeatedly to exhibit genotoxicity in tests for unscheduled DNA systhesis (UDS) in cultured primary rat hepatocytes. Benzene is consistently negative in HeLa cells with or without metabolic activation. Glauert *et al.*⁽⁵⁰⁾ published the single positive report for increased UDS in cultured primary rat hepatocytes associated with benzene exposure.

In a study of *in vitro* DNA damage, mouse L5178 YS lymphoma cells failed to show single strand breaks after exposure to 1.0 mM benzene, phenol, or catechol or to 0.1 mM hydroquinone; however, a dose-dependent increase in DNA damage was observed after treatment with para-benzoquinone or 1,2,4-benzenetriol. Para-benzoquinone at 6 µM induced 70 percent single strand DNA breaks within 3 minutes of exposure; the same damage was achieved by benzenetriol within 60 minutes. (51)

A concentration-dependent increase in mouse peripheral blood micronuclei was observed after C57BL/6 mice inhaled 10, 25, 100, or 400 ppm, 6 hours per day, for 9 days. (52) When C57BL/6 mice inhaled 300 ppm benzene for 16 weeks under a similar protocol and the patterns for micronucleus induction monitored, the initial increase was followed by a gradual decrease. (53) When the peripheral blood of B6C3F1 mice given oral benzene(17) was studied, a dose-dependent increase in the numbers of circulating erythrocyte micronuclei occurred. A significant increase was observed in male mice given a dose as low as 25 mg/kgday for 120 days. (54) Pretreatment of male and female CD-1 mice with metabolic enzyme-inducing agents (phenobarbital, SKF-525A, Arochlor 1254) failed to protect against the clastogenic effect of benzene exposure, but pretreatment with 3-methylcholanthrene potentiated benzene myeloclastogenicity. (55) Male mice were more sensitive than female mice and chromosomal damage was greater after oral than after intraperitoneal administration. (55)

Chromosome aberrations were induced in Wistar rats

after inhalation of 100 or 1000 ppm benzene. (56) When male DBA/2 mice inhaled benzene at 0, 10, 100, or 1000 ppm or male Sprague–Dawley rats inhaled benzene at 0, 0.1, 0.3, 1, 3, 10, or 30 ppm for 6 hours, significant (dose-dependent) increases in SCE and micronuclei were observed in mice at \geq 10 ppm, and increased SCE and micronuclei were observed in rats inhaling \geq 3 ppm and at 1 ppm, respectively. (57) The Erexson data (57) are the lowest concentrations of inhaled benzene that have been reported to induce genotoxicity.

Neoplastic Transformation

Using morphologically transformed colonies as a marker, benzene was considered mutagenic in Syrian hamster embryo (SHE) cells, but it was not considered mutagenic in cultured Balb/C 3T3 mouse fibroblasts, in Simian adenovirus-transformed SHE cells, and in Chinese hamster ovary (CHO) cells. Benzene, hydroquinone, and para-benzoquinone were reported to alter gene expression in cultured Swiss mouse spleen lymphocytes, where hydroquinone and para-benzoquinone at 10–20 µM inhibited RNA synthesis 50 percent. Inhibition of T-cell proliferation and reduced production of interleukin-2 (a T-cell growth factor) by 5 µM para-benzoquinone was suggested to account, in part, for benzene-induced aplastic anemia.

Human Cytogenicity

Forni et al. (60) found a significant increase in lymphocyte chromosome aberrations in two groups of workers with overt benzene intoxication as compared to age-matched controls. One group consisted of 25 individuals recovered from benzene hemopathy 1-18 years previous along with 4 additional workers currently suffering from acute benzene poisoning. The second group consisted of 34 workers in a rotogravure plant exposed at 125-532 ppm benzene in air from 1952 to 1953. Tough et al. (61,62) found an increased incidence of chromosome aberrations in 38 workers inhaling 25-150 ppm benzene for 1-25 years compared to the incidence in the general human population. These individuals had been exposed to benzene until two to four years prior to the study. (61,62) Watanabe et al. (63) found an increase in the frequency of SCE among nine females at six onths after cessation of benzene exposure at 1-9 ppm for 1-20 years and among seven females exposed to benzene at 3-50 ppm for 2-12 years. Killian and Daniel⁽⁶⁴⁾ found a significant increase in chromosomal aberrations among workers exposed to average benzene levels below 10 ppm. Workers exposed to benzene (average, 56.6 months) had a doubling of chromosomal breaks and a threefold increase in rings and dicentric chromosomes. Almost twice as many benzene-exposed workers as controls exhibited both chromosome breaks and rings and dicentric chromosomes.(64)

Picciano^(65,66) examined the Killian and Daniel⁽⁶⁴⁾ data and reported that 38 (73.1%) of 52 workers exposed to mean ambient benzene at less than 10 ppm had chromosome breaks as compared with 18 (40.9%) of 44 matched (unexposed) controls. When individuals with both chro-

mosome breaks and chromosome markers (rings, dicentric chromosomes) were compared, less than 3 percent of the nonexposed group showed genetic damage where 2^{-7} percent of the exposed workers were afflicted with chromosome aberrations (p < 0.001).

A number of reports suggests that benzene-induced human chromosome damage is site-specific. Ding et al. (67) reported a cytogenetic study of 21 patients (8 male and 13 female) with chronic benzene poisoning who had been exposed to unspecified benzene concentrations for 1-28 years (average, 6 years). At the time of cytogenetic analyses, all individuals had not been exposed for 5-20 years (average, 10 years), and all but one had recovered from clinical signs of benzene poisoning. Hypodiploid and hyperdiploid cells were increased significantly in the benzeneexposed patients, and chromosome deletions in the hypodiploid cells involved groups C, E, and G chromosomes and chromosome gains in the hyperdiploid cells involved groups C and E. Similar findings were also reported by Sasiadek and Jagielski⁽⁶⁸⁾ where chromosomal aberrations were detected more frequently in chromosomes 2 (Group A), 4 (Group B), and 6 and 9 (both are Group C). Sarto and associates (69) found an increase in chromosome aberrations among 22 workers inhaling 0.2-12.4 ppm benzene for 11.4 ± 7.0 years; a control population was matched for sex, age, smoking habits, and site of residence.

Pharmacokinetic/Metabolism Studies

Rusch *et al.*⁽⁷⁾ concluded that humans absorb approximately 46 percent of the benzene that is inhaled. Assuming a respiratory rate of 16 per minute and a tidal volume of 0.5 liters, approximately 7.5 µL benzene can be expected to be absorbed each hour through the lungs of a person inhaling air containing 10 ppm benzene.⁽⁷⁾

Benzene dermal absorption was 0.05 percent when neat liquid benzene was applied directly to a human forearm

at 0.0022 mg/cm² and allowed to dry; (70) and the flux of benzene through cultured human abdominal skin from air saturated with benzene at 31°C was 1.0 μL cm⁻²-hr⁻¹.⁽⁷¹⁾ Susten et al.(72) found that after dermal application of 5 μL¹⁴C-labeled benzene to intact skin of hairless mice, maximal skin radioactivity occurred at 1.5 min, and it remained "essentially unchanged for at least 2.5 hr." Permeability is, however, dependent upon presence of solvents. Blank and McAuliffe⁽⁷¹⁾ found the constants to be 111, 3.73, 2.4, and 1.4 \times 10⁻³ μ L cm⁻²•hr⁻¹, respectively, for water, hexadecane, isooctane, hexane, and gasoline. Based on in vitro percutaneous absorption and in vivo inhalation data, one example of calculated total benzene exposure used an adult working in ambient air containing 10 ppm benzene with 100 cm² skin surface in direct contact with gasoline containing 5 percent benzene. It was estimated that if the worker's entire skin surface was in contact with ambient air, the individual would absorb 7.5 µL benzene via inhalation in one hour, 7.0 µL from direct dermal contact with gasoline, and 1.5 µL from body surface exposure to ambient air.(71)

Sabourin *et al.*⁽⁷³⁾ investigated the absorption and elimination of benzene in F344/N rats, Sprague–Dawley rats, and B6C3F1 mice after an oral or intraperitoneal dose of 0.5–150 mg/kg. They reported that gastrointestinal absorption was essentially complete.

The toxicity of benzene has been attributed to its metabolites.⁽⁷⁴⁾ A major metabolite is phenol (Figure 1), generated by oxidation of benzene by the liver cytochrome microsomal system⁽⁷⁵⁾ via the reactive epoxide intermediate, benzene oxide. Results of physiologically based pharmacokinetic modeling of benzene metabolism found that mice metabolized a greater proportion of absorbed benzene to the hydroquinone conjugates and muconic acid than did rats.⁽⁷⁶⁾ Rats metabolized benzene primarily to the phenyl conjugates and to the phenyl mercapturic

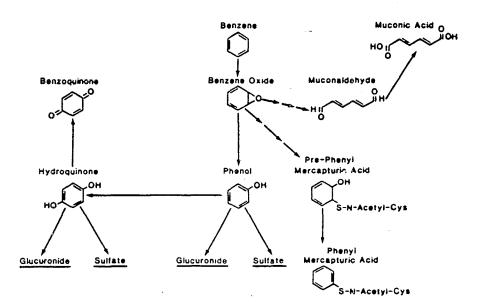


FIGURE 1. Major pathways of benzene metabolism. (Reproduced with permission from reference 76.)

acids.(76) Although bone marrow enzymes are not efficient for benzene metabolism, phenol can be metabolized in marrow via myeloperoxidase.(77) Benzene metabolism to phenol, formation of water-soluble phenyl glucuronide and sulfate conjugates, and conjugation with glutathione and urinary elimination of benzene as the phenylmercapturic acid are considered detoxication pathways. Microsome ring-opening reactions giving rise to the reactive mucondialdehyde yield muconic acid, a pathway considered responsible for at least some aspects of benzene toxicity. Hydroxylation of phenol generates hydroquinone; dehydrogenation of benzene dihydrodiol generates catechol. (78,79) Hydroquinone and catechol can accumulate in bone marrow and lymphoid tissues; (80) hydroquinone can oxidize spontaneously in vitro to para-benzoquinone under physiologic conditions. (81,82) Catechol does not oxidize spontaneously under these conditions; however, it can be metabolized (presumably the cytochrome P-450 system) to 1,2,4-benzenetriol. (83) The toxicity of hydroquinone and 1,2,4-benzenetriol involves free radical formation via superoxides; covalent binding of the semiquinones to DNA, RNA, and other cellular components; and direct alkylation of sulfhydryl groups by para-benzoquinone or its derivatives. Hydroquinone and benzoquinone were the most toxic metabolites to cultured bone marrow stromal cells, where catechol and benzenetriol inhibited colony growth only at very high benzene doses to male B6C3F1 mice. (80) Injury to bone marrow stromal cells has been implicated as a precursor step to benzene hematotoxicity. (80) A recent symposium on benzene metabolism, toxicity, and carcinogenesis(84) provides an authoritative summary on benzene biotransformation and the implication for human health risk assessment.

Human Studies

As an acute poison, benzene produces narcotic effects comparable to those of toluene. Benzene is considered very toxic; probable human oral lethal dose would be between 50–500 mg/kg (1 tsp to 1 oz).⁽⁸⁵⁾ Human inhalation of approximately 20,000 ppm (2% in air) was fatal in 5–10 minutes.⁽⁸⁶⁾

Aksov et al. (87-89) studied 28,500 Turkish shoe and handbag production workers who inhaled an average of 150-210 ppm when benzene-containing adhesives were used and 15-30 ppm at other times. Peak benzene exposures varied between 210 and 640 ppm, and the duration of exposure was estimated to average 9.7 years. Of the 44 cases of pancytopenia, 23 (52%) experienced remission of the aplastic anemia, 14 (32%) died from complications of aplastic anemia or pancytopenia, and 6 (14%) later died from leukemia. Of 42 leukemia cases, 26 percent were preceded by a 6-month to 6-year period of pancytopenia prior to the onset of leukemia. Aksov^(90,91) reported an update to the above cohort to the year 1983, wherein a total of 73 patients chronically exposed to benzene were examined. Fifty-one of the 73 had leukemia, 12 had malignant lymphoma, 4 had multiple myeloma, and 6 had

lung cancer. Among the 51 leukemic patients, 20 were afflicted with acute myeloblastic leukemia, 7 were considered preleukemic, 20 were diagnosed with acute erythroleukemia, 5 had acute myelomonocytic leukemia, and 1 was diagnosed as an acute undifferentiated leukemia. Thirteen of the 51 leukemic patients had suffered pancytopenia; the average duration of benzene exposure was 9.93 years.

Vigliani ⁽⁹²⁾ studied groups of workers employed in rotogravure plants, shoe factories, and other industries where benzene was used as a solvent. Benzene concentrations in air near the rotogravure machines were 200–400 ppm, with peak values as high as 1500 ppm. Sixty-six cases of benzene hemopathy were observed, and of the 18 deaths in this group, 7 died of aplastic anemia and 11 died of leukemia. In a second group of workers where ambient benzene ranged from 25–600 ppm, 135 workers with benzene hemopathy were studied. Of the 135, 16 died (3 from aplastic anemia and 13 from leukemia).

Infante et al. (93) reviewed death certificates for a cohort of 748 white male workers who had been occupationally exposed to benzene from 1940-1949; exposures are not known precisely but ranged up to 100 ppm. (94) Others (95) cite reports that peak exposures may have been as high as 200-350 ppm. Vital status was followed up to 1973. A fivefold excess risk of all leukemias was reported, and a tenfold excess of deaths from myelogenous and monocytic leukemias was observed. In a follow-up through June 30, 1975, Rinsky et al. (96) reported 7 deaths from leukemia versus 1.25 expected (standardized mortality ratio [SMR] = observed no. deaths/expected no. deaths = 560). When compared by length of employment, there was a significant excess of leukemia observed among workers employed five or more years, but not among those employed less than five years. Two workers died from leukemia among the group employed less than five years compared to 1.02 expected (not statistically significant). Among those employed for five or more years, five died from leukemia compared to 0.23 expected (SMR = 2100). Short-term area samples measured between 1946 and 1976 indicated that most benzene levels were below 100 ppm and some were above 100 ppm. (95,96) Rinsky et al. (96) cite documents indicating that these workers were required to wear respirators (efficiency not stated) when exposed (even momentarily) to concentrations greater than the TWA (ranging to a maximum allowable concentration of 100 ppm in 1941 to an 8-hour TWA of 10 ppm from 1969 on). For those individuals with more than ten years of employment, three leukemia deaths were observed as compared to 0.09 expected (SMR = 3300). Cumulative benzene exposure was calculated for each member of the benzene cohort in ppmyears, and the cohort follow-up was extended to 1982.(.7) A total of 1165 white males with at least one ppm-day of cumulative benzene exposure (to December 31, 1965) were included in the cohort for a total of 31,612 person-years at risk. Fifteen deaths in this cohort were observed from lymphatic and hemopoietic cancers versus 6.6 expected (SMR = 227). Nine cases of leukemia were observed com-

pared to 2.7 expected (SMR = 337), and four cases of multiple myeloma were observed compared to one expected (SMR = 409) [all cases statistically significant]. Rinsky et al. (97) determined that cumulative exposure to benzene (measured as ppm-years) was the most reliable predictor of death from benzene-induced leukemia. Increases in cumulative exposure were associated with marked progressive increases in the SMR for leukemia: among workers with less than 40 ppm-years cumulative exposure, the SMR = 109; with 40 to 199.99 ppm-years cumulative exposure, the SMR = 322; with 200 to 399.99 ppm-years cumulative exposure, the SMR = 1186; and with 400 or more ppm-years, the SMR = 6637. (The ppm-years were calculated as 40 years at 10 ppm average exposure/year = 400 ppm-years.) Seven of the nine leukemia deaths with multiple myeloma had less than 40 ppm-years of benzene exposure. Rinsky et al. (97) concluded that protection from benzene-induced leukemia increased exponentially with reductions in exposure time.

Yin et al. (98) conducted a retrospective cohort study of 28,460 workers exposed to 3–308 ppm benzene (with the majority exposed to 15-150 ppm) compared to a control cohort of 28,257 workers not known to be exposed to benzene. Thirty cases of leukemia were found in the exposed population compared to four such cases in the control. The benzene cohort experienced a leukemia mortality rate of 14 per 100,000 person-years, and the control population experienced a leukemia mortality rate of 2 per 100,000 person years (SMR = 5.74). In an additional study authored by Yin and associates, (99) ambient benzene concentrations for 508,818 workers averaged 5.6 ppm with 65 percent of the workplaces having less than 12 ppm and 1.3 percent having benzene levels greater than 308 ppm. Aplastic anemia occurred at 12.1 per 100,000 persons in this cohort and represented a 5.8-fold increase over that of the general population.

Ott *et al.*⁽¹⁰⁰⁾ carried out a mortality study of 594 white male workers exposed to benzene from 1940–1970. The Occupational Safety and Health Administration (OSHA)⁽¹⁰¹⁾ concluded that the Ott cohort was exposed to an average of 5 ppm for an average of nine years. Three cases of myelocytic leukemia (2 classified as acute) were found compared to 0.8 cases expected (p < 0.047). Bond *et al.*⁽¹⁰²⁾ extended the cohort definition for the Ott study to include those employees who worked for at least one month (1938–1978) and increased the observation follow-up to 1982, bringing the total persons studied to 956. Four deaths due to myelogenous leukemia were observed with 0.9 expected (SMR = 444).

Decoulle *et al.*⁽¹⁰³⁾ found a fourfold excess risk for lymphatic and hematopoietic cancers among oil refinery and chemical plant workers exposed to benzene. The exposures were very poorly documented, but they resulted primarily from plant fugitive emissions and perhaps accompanied by gross exposures from cleaning tools, hands, and clothing with liquid benzene. The historical cohort mortiality study of 259 male employees found four deaths from lymphoreticalar cancers compared to 1.1 expected

(SMR = 364), and three deaths due to leukemia where 0.4 were expected. The multiple myelomas observed here, taken together with previous reports of benzene-associated myeloma, prompted the suggestion that the pathogenesis of human multiple myeloma and chronic lymphatic leukemia may arise from damage to B-cell lineage. (103) Wong(104.105) divided the benzene exposure for 4602 workers (minimum time of 6 months) into four categories: < 1 ppm; 1–10 ppm; 11–50 ppm; and 50 ppm, with peak exposures of < 25 ppm, 25-100 ppm, and > 100 ppm. He compared their mortality with that of 3074 employees from the same or similar plants who had no known occupational benzene exposure. When all lymphatic and hemotopoietic cancers were considered, there was a significantly elevated risk (p = 0.03) for benzene-exposed white males when compared to unexposed workers. There was a significant concentration-dependent increase for all lymphohematopoietic cancers (p = 0.02), for leukemia (p = 0.01), with borderline significance (p = 0.057) for non-Hodgkin's lymphopoietic cancers. Prolonged cumulative exposures were judged more important for human benzene carcinogenicity than maximum peak exposures, and the authors (104,105) concluded that there was a significant association between occupational benzene exposure and the occurrence of leukemia, all lymphopoietic cancers, and non-Hodgkin's lymphopoietic cancers.

A number of epidemiologic studies (106.117) have considered the mortality and cancer incidence among petroleum and rubber workers. Most of these studies, however, failed to quantify the benzene exposures adequately, failed to determine whether the toxicity reported was indeed associated with benzene exposures, and were confounded by difficulties in confirming the validity of the diagnoses upon which the SMR and other risk estimates were made.

The latency period for benzene induction of human leukemia varies from 2 to 50 years. Aksoy *et al.*^(87–91) found that the induction period ranged from 6 to 14 years (median, 11 years). Vigliani⁽⁹²⁾ reported an induction period of 3 to 23 years (median, 9 years), and Rinsky⁽⁹⁶⁾ indicated a median latency of 12 years (2–22 years). The Shell Oil study⁽¹¹³⁾ indicated a latency of 17–54 years between the date of hire and date of death from leukemia. Yin⁽⁹⁸⁾ estimated the average latency time for benzene-induced leukemia as 11.4 years. The 1985 OSHA report⁽¹⁰¹⁾ concluded that 11 years was a reasonable estimate for the average duration of leukemia induction associated with occupational benzene exposure.

Basis of the TLV

Although benzene has long been recognized as a myelotoxicant (e.g., more than 140 fatalities due to benzene poisoning were recorded in the open scientific literature prior to 1959), the carcinogenic activity of chronic exposure to relatively low ambient concentrations of benzene in workplace air was not recognized until the last ten years. Benzene is a human and rodent clastogen and carcinogen. Adverse health effects in animals exposed to benzene mir-

ror those reported in humans, with exposure at 1 ppm benzene and above inducing measurable cytogenetic damage. (57) Women inhaling 1–9 ppm exhibited increased lymphocyte chromosome aberrations, (63) and significant elevations in chromosomal aberrations have been corroborated among workers inhaling benzene at mean concentrations less than 10 ppm. (64–66)

Several quantitative human health risk assessments have been carried out in an attempt to define the concentrations of benzene in air that are associated with lifetime excess cancer risk,⁽²⁾ but these methods are problematic, particularly when attempting to extrapolate quantitative animal data to the human. Notable has been their failure to incorporate the differential metabolic disposition and known pharmacokinetic parameters for rodents⁽⁷⁶⁾ compared to human beings. The rodent carcinogenicity data support the designation of benzene as a known human carcinogen.

Theoretical estimates of excess cancer risk can be calculated using any of a variety of statistical models, including the linearized "multistage" (which does not describe biologic initiation/promotion phenomena), the one-hit, Weibull, logit, or probit models; however, there is no current understanding of the biochemical mechanisms involved in benzene-induced leukemia and other cancers to show that any one of these methods is any more accurate than another. Because of the different assumptions that must be made for use of the different models, the theoretical estimates of excess cancer risk that result can differ by orders of magnitude. White et al. (118) used a linear, nonthreshold model to describe the benzene dose-response human carcinogenicity data and calculated that at 10 ppm benzene, 44–152 excess cases of leukemia per 1000 exposed workers would occur, and that at 1 ppm benzene, 5-16 such excess case would occur. The International Agency for Research on Cancer (IARC)(115) used a similar approach and published theoretical excess cancer risk estimates of 14-140 excess cases per 1000 individuals exposed at 10 ppm, and 1.4-14 excess cases among 1000 individuals exposed at 1 ppm. Crump and Allen(2,119) carried out quantitative analyses of the epidemiologic data gathered by Rinsky et al., (96,97) Ott el al., (100) and Wong et al. (104,105) After 45 years (working lifetime) exposure at 10 ppm benzene, Crump and Allen(119) calculated 95 theoretical excess leukemia deaths per 1000 workers. Exposure at 1 ppm was calculated as associated with 10 theoretical excess leukemia deaths per 1000 workers. Although such estimates have been preferred in the legal arena,(2) these methods remain the subjects of severe criticism. (2,129,121)

Because of the acknowledged high quality of the epidemiologic data, (2) direct inspection of these data can provide the basis for the benzene TLV. The Dow Chemical Company study (100) "demonstrates a significant fourfold increase in myelogenous leukemia for workers who had been exposed to average benzene concentrations of about 5 ppm for an average of about nine years" and "two out of the four individuals in the study who died from leukemia were characterized as having been exposed to average benzene levels below 2 ppm." (2)

The risk assessment for benzene and leukemia is based on the human data. Rinsky et al. (97) provided the most authoritative examination of the known odds of death from benzene-induced leukemia. For a worker exposed at average daily benzene concentrations of 10 ppm for 45 years, the odds of death from leukemia were 290 times that of an unexposed worker. For an individual inhaling 1 ppm for 45 years, the odds of benzene-induced leukemic death were 1.7 times that of an unexposed worker. For an individual inhaling 0.5 ppm for 45 years, the odds of benzene-induced leukemic death were 1.3 times that of an unexposed worker. Using these data, the odds of benzeneinduced leukemic death at 0.1 ppm approach very nearly the odds of leukemic death for a worker who is not exposed to benzene. Accordingly, a TLV-TWA of 0.1 ppm benzene is recommended. A STEL is not recommended. The reader is encouraged to review the section on Excursion Limits in the "Introduction to the Chemical Substances" of the current TLV/BEI Booklet for guidance and control of excursions above the TLV-TWA even when the 8-hour TWA is within recommended limits. The recommended TLV of 0.1 ppm is less than the concentration associated with genetic damage in animals, (57) and it is less than the concentrations associated with genetic damage in human beings. (63) As calculations show that benzene dermal absorption can contribute substantially to the total absorbed benzene dose, (71) the skin designation is appropriate.

BEI Indication

Biological monitoring for human benzene exposure at ambient concentrations less than 1 ppm can be most readily documented by determination of urinary S-phenylmer-capturic acid (Figure 1).⁽¹²²⁾ The mercapturic acid conjugate is formed and excreted together with phenol, catechol, hydroquinone, and hydroxy hydroquinone. It is a urinary metabolite of high specificity for occupational benzene exposure giving reliable indication of exposures at the 0.1–0.15 ppm range, whereas urinary phenol is not reliable unless gross benzene exposure has occurred.⁽¹²²⁾

The lowest practical detection limit, in the absence of interfering substances, has been reported at concentrations at least as low as 0.1 ppm. In the presence of interfering vapors, the accuracy and reliability of workplace air monitoring at ambient benzene concentrations even above 1.0 ppm can be questioned.

References

- Synder, R.: The Benzene Problem in Historical Perspective. Fundam. Appl. Toxicol. 4:692–699 (1984).
- Occupational Safety and Health Administration: 29 CFR Part 1910, Occupational Exposure to Benzene; Final Rule. Part II, Department of Labor. Fed. Reg. 52(176):34460–34578 (September 11, 1987).
- Ward, C.O.; Kuna, R.A.; Snyder, N.K.; et al.: Subchronic Inhalation Toxicity of Benzene in Rats and Mice. Am. J. Ind. Med. 7:457–473 (1985).
- Uyeki, E.M.; Ashkar, A.E.; Shoeman, D.W.; Bisel, T.V.: Acute Toxicity
 of Benzene Inhalation in Hemopoietic Precursor Cells. Toxicol. Appl.
 Pharmacol. 40:49–57 (1977).
- 5. Gill, D.D.; Jenkins, V.J.; Kempen, R.E.; Ellis, S.: The Importance of

- Pluripotent Stem Cells in Benzene Toxicity, Toxicology 16:163–171 (1980).
- Green, J.D.: Snyder, C.A.: LoBue, J.: et al.: scute and Chronic Dose-Response Effects of Inhaled Benzene on Multipotential Engatopoietic Stem (CFU-S) and Granulocyte/Macrophage Progenitor (GM CFU-C) Cells in CD-1 Mice. Toxicol. Appl. Pharmacol. 58:492–503 (1981).
- Rusch, G. M.; Leong, B.K.; Laskin, S.; Benzene Metabolism, J. Toxicol. Environ. Health 2:23–36 (19⁻⁻⁻).
- Cronkite, E.P.: Drew, R.T.: Inove, T.; Bullis, J.E.: Benzene Hematotoxicity and Leukemogenesis. Am. J. Ind. Med. 7:447–456 (1985).
- Cronkite, E.P.: Chemical Leukemogenesis: Benzene as a Model. Seminar Hematol. 24:2–11 (1987).
- Rozen, M.G.; Snyder, C.A.: Protracted Exposure of C57BL/6J Mice to 300 ppm Benzene Depresses B- and T-Lymphocyte Numbers and Mitogen Responses. Evidence for Thymic and Bone Marrow Proliferation in Response to the Exposures. Toxicology 37:13–26 (1985).
- Aoyama, K.: Effects of Benzene Inhalation on Lymphocyte Subpopulations and Immune Response in Mice. Toxicol. Appl. Pharmacol. 85:92–101 (1986).
- Rozen, M.G.; Snyder, C.A.; Albert, R.E.: Depression in B- and T-Lymphoxyte Mitogen-induced Blastogenesis in Mice Exposed to Low Concentrations of Benzene. Toxicol. Lett. 20:343–349 (1984).
- Snyder, C.A.; Goldstein, B.D.; Sellakumar, A.; et al.: Hematotoxicity of Inhaled Benzene to Sprague—Dawley Rats and AKR Mice at 300 ppm. J. Toxicol. Environ. Health 4:605–618 (1978).
- Snyder, C.A.; Goldstein, B.D.; Sellakumar, A.R.; et al.: The Inhalation Toxicology of Benzene: Incidence of Hematopoietic Neoplasms and Hematotoxicity in AKR/J and C57BL/6J Mice. Toxicol. Appl. Pharmacol. 54:323–331 (1980).
- Maltoni, C.; Scarnato, C.: First Experimental Demonstration of the Carcinogenic Effects of Benzene: Long-term Bioassays on Sprague– Dawley Rats by Oral Administration. Med. Lav. 70:352–357 (1979).
- Maltoni, C.; Conti, B.; Cotti, G.; Belpoggi, F.: Experimental Studies on Benzene Carcinogenicity of The Bologna Institute of Oncology: Current Results and Ongoing Research. Am. J. Ind. Med. 7:415

 –446 (1985).
- National Toxicology Program: NTP Technical Report on the Toxicology and Carcinogenesis Studies of Benzene (CAS No. 71-43-2) in F344/N Rats and B6C3F1 Mice (Gavage Studies). NTP TR 289. DHHS (NIH) Pub. No. 86-2545. Research Triangle Park, NC (1986).
- Cronkite, E.P.: Benzene Hematotoxicity and Leukemogenesis. Blood Cell. 12:129–131 (1986).
- Schwetz, B.A.: A Review of the Developmental Toxicity of Benzene.
 In: Advances in Modern Environmental Toxicology, Vol. IV, Carcinogenicity and Toxicity of Benzene, pp. 17–21. M.A. Mehlman, Ed. Princeton Scientific, Princeton, NJ (1983).
- Litton Bionetics, Inc.: Unpublished data, November 1977 and December 1978, Kensington, MD; cited in B.A. Schwetz, 21.
- Kura, R.A.; Kapp, R.W.: The Embryotoxic/Teratogenic Potential of Benzene Vapor in Rats. Toxicol. Appl. Pharmacol. 57:1–7 (1981).
- Coate, W.B.; Hoberman, A.M.; Durloo, R.S.: Inhalation Teratology Study of Benzene in Rats. Adv. Modern Environ. Toxicol. 6:187–198 (1984).
- Keller, K.A.; Snyder, C.A.: Mice Exposed in utero to Low Concentrations of Benzene Exhibit Enduring Changes in Their Colony-forming Hematopoietic Cells. Toxicology 42:171–181 (1986).
- Ungvary, G.; Tatrai, E.: On the Embryotoxic Effects of Benzene and Its Alkyl Derivatives in Mice, Rats and Rabbits. Arch. Toxicol. 8:425–430 (1985).
- Dean, B.J.: Recent Findings on the Genetic Toxicology of Benzene, Toluene, Xylene and Phenols. Mutat. Res. 154:153–181 (1985).
- Lebowitz, H.; Brusick, D.; Matheson, D.; et al.: Commonly Used Fuels and Solvents Evaluated in a Battery of Short-term Bioassays. Environ. Mutagen. 1:172–173 (1979).
- Bartsch, H.; Malaveille, C.; Camus, A.M.; et al.: Validation and Comparative Studies on 180 Chemicals with S. hphimurium Strains and V79 Chinese Hamster Cells in the Presence of Various Metabolizing Systems. Mutat. Res. 76:1–50 (1980).
- 28, Nestmann, E.R.; Lee, E.G.H.; Matula, T.I.; et al.: Mutagenicity of Con-

- stituents Identified in Pulp and Paper Milk Effluents Using the Salmonella/Mammalian-Microsome Assay, Mutat. Res. 79,203–212 (1980).
- Shimizu, M.; Yasui, Y.; Matsumoto, N.: Structural Specificity of Aromatic Compounds with Special Reference to Mutagenic Activity in Sulmonella applimurium: A series of Chloro- or Fluoro-Nitrobenzene Derivatives, Mutat. Res. 116:217–238 (1983).
- McCarroll, N.E.: Piper, C.E.: Keech, B.H.: Bacterial Microsuspension Assays with Benzene and Other Organic Solvents. Environ. Mutagen. 2:281–282 (1980).
- McCarroll, N.E.: Piper, C.C.: Keech, B.H.: An E. coli Microsuspension Assay for the Detection of DNA Damage Induced by Direct-acting Agents and Promutagens. Environ. Mutagen. 3:429–444 (1981).
- McCarroll, N.E.; Keech, B.H.; Piper, C.E.: A Microsuspension Adaptation of the *Bacillus subtilis* 'rec' Assay. Environ. Mutagen. 3:607–616 (1981).
- Rozenkranz, H.S.; Leifer, Z.: Determining the DNA Modifying Activity
 of Chemicals Using the DNA Polymerase-Deficient *Escherichia coli*.
 In: Chemical Mutagens: Principles and Methods for their Detection,
 Vol. 6, pp. 109–147. F.J. deSerres and A. Hollaender, Eds. Plenum,
 New York (1980).
- 34. Parry, J.M.: Summary Report on the Performance of the Yeast and Aspergillus Assay. In: Evaluation of Short-Term Tests for Carcinogens: Report of the International Program on Chemical Safety Collaborative Study on *In Vitro* Assays, pp. 25–46. J. Ashby, F.J. deSerres, M. Draper, et al., Eds. Elsevier, Amsterdam (1985).
- 35. Parry, J.M.: Eckardt, F.J.: The Induction of Mitotic Aneuploidy, Point Mutation and Mitotic Crossing-over in the Yeast, Saccbaromyces cerevisiae Strain D61-M and D6. In: Evaluation of Short-Term Tests for Carcinogens: Report of the International Program on Chemical Safety Collaborative Study on In Vitro Assays, pp. 261–269. J. Ashby, F.J. deSerres, M. Draper, et al.: Eds. Elsevier, Amsterdam (1985).
- Nylander, P.O.; Olofsson, H.; Rasmuson, B.; Savahlin, H.: Mutagenic Effects of Petrol in *Drosophila melanogaster*. I. Effects of Benzene and 1,2-Dichloroethane. Mutat. Res. pp. 163–167 (1978).
- Kale, P.G.; Baum, J.W.: Genetic Effects of Benzene in Drosophila melanogaster Males. Environ. Mutagen. 5:223–226 (1983).
- 38. Vogel, E.W.: Summary Report on the Performance of the *Drosophila* Assays. In: Evaluation of Short-Term Tests for Carcinogens: Report of the International Program on Chemical Safety Collaboration Study on *In Vitro* Assays, pp. 47–57. J. Ashby, F.J. deSerres, M. Draper, et al., Eds. Elsevier, Amsterdam (1985).
- 39. Fujikawa, K.; Ryo, H.; Kondo, S.: The *Drosophila* Gene Mutation and Small Deletion Assay Using the Zeste-White Somatic Eye Colour System. In: Evaluation of Short-Term Tests for Carcinogens: Report of the International Program on Chemical Safety Collaborative Study on *In Vitro* Assays, pp. 319–324. J. Ashby, F.J. deSerres, M. Draper, et al., Eds. Elsevier, Amsterdam (1985).
- 40. Vogel, E.W.: The *Drosopbila* Somatic Recombination and Mutation Assay Using the White-Coreal Somatic Eye Colour System. In: Evaluation of Short-Term Tests for Carcinogens: Report of the International Program on Chemical Safety Collaborative Study on *In Vitro* Assays, pp. 313–317, J. Ashby, F.J. deSerres, M. Draper, et al., Eds. Elsevier, Amsterdam (1985).
- Lyang, J.C.; Hsu, T.C.; Henry, J.E.: Cytogenetic Assays for Mitotic Poisons: The Grasshopper Embryo System for Volatile Liquids. Mutat. Res. 113:467–479 (1983).
- 42. Garner, R.C.: Summary Report on the Performance of Gene Mutation Assays in Mammalian Cells in Culture. In: Evaluation of Short-Term Tests for Carcinogens: Report of the International Program on Chemical Safety Collaborative Study on *In Vitro* Assays, pp. 85–94. J. Ashby, F.J. deSerres, M. Draper, et al., Eds. Elsevier, Amsterdam (1985).
- Howard, C.A.; Sheldon, T.; Richardson, C.R.: Chromosomal Analysis
 of Human Lymphocytes Exposed in vitro to Five Chemicals. In:
 Evaluation of Short-Term Tests for Carcinogens: Report of the International Program on Chemical Safety Collaborative Study on In
 Vitro Assays, pp. 457–467. J. Ashby, F.J. deSerres, M. Draper, et al.,
 Eds. Elsevier, Amsterdam (1985).
- 44. Danford, N.D.: Tests for Chromosome Aberrations and Aneuploidy in the Chinese Hamster Fibroblast Cell Line CH1-L. In: Evaluation of Short-Term Tests for Carcinogens: Report of the International

- Program on Chemical Safety Collaborative Study on *In Vitro* Assays, pp. 397–411. J. Ashby, F.J. de Serres, M. Draper, et al., Eds. Elsevier, Amsterdam (1985).
- Morimoto, K.; Wolff, S.; Koizumi, A.: Induction of Sister-Chromatid Exchanges in Human Lymphocytes by Microsomal Activation of Benzene Metabolites. Mutat. Res. 119:355-360 (1983).
- Morimoto, K.; Wolff, S.: Increase of Sister Chromatid Exchanges and Perturbations of Cell Division Kinetics in Human Lymphocytes by Benzene Metabolites. Cancer Res. 40:1189–1193 (1980).
- Morimoto, K.: Induction of Sister Chromatid Exchanges and Cell Division Delays in Human Lymphocytes by Microsomal Activation of Benzene. Cancer Res. 43:1130–1334 (1983).
- Erexson, G.L.; Wilmer, J.L.; Kligerman, A.D.: Sister Chromatid Exchange Induction of Human Lymphocytes Exposed to Benzene and Its Metabolites in vitro. Cancer Res. 45:2471–2477 (1985).
- Tice, R.R.; Vogt, T.F.; Costa, D.L.: Effect of Sex, Strain, Age and Route of Exposure on Benzene-induced Sister Chromatid Exchange (SCE) in Murine Bone Marrow. Environ. Mutagen. 3:338–339 (1981).
- Glauert, H.P.; Kennan, W.S.; Sattler, G.S.; Pitot, H.C.: Assays to Measure the Induction of Unscheduled DNA Synthesis in Cultured Hepatocytes. In: Evaluation of Short-Term Tests for Carcinogens: Report of the International Program on Chemical Safety Collaborative Study on *In Vitro* Assays, pp. 371–373. J. Ashby, F.J. deSerres, M. Draper, et al., Eds. Elsevier, Amsterdam (1985).
- Pellack-Walker, P.; Blumer, J.L.: DNA Damage in L5178YS Cells Following Exposure to Benzene Metabolites. Molec. Pharmacol. 30:42–47 (1983).
- Tice, R.R.; Sawey, M.J.; Drew, R.T.; Cronkite, E.P.: Benzene-induced Micronuclei in the Peripheral Blood of Mice: A Retrospective Analysis. Environ. Mutagen. 6:421 (1984).
- Luke, C.A.; Tice, R.R.; Drew, R.T.: Duration and Regimen Induced Micronuclei in the Peripheral Blood of Mice Exposed Chronically to Benzene. Environ. Mutagen. 7(Suppl. 3):29 (1985).
- Choy, W.N.; MacGregor, J.T.; Shelby, M.D.; Maronpot, R.R.: Induction of Micronuclei in the Peripheral Blood of Mice Exposed Chronically to Benzene. Mutat. Res. 143:55–59 (1985).
- Gad-El-Karim, M.M.; Harper, B.J.; Legator, M.S.: Modification in the Myeloclastogenic Effect of Benzene in Mice with Toluene, Phenobarbital, 3-Methylcholanthrene, Arochlor 1254 and SKF-525A (Proadifen Hydrochloride). Mutat. Res. 135:225–243 (1984).
- Styles, J.A.; Richardson, C.R.: Cytogenetic Effects of Benzene: Dosimetric Studies on Rats Exposed to Benzene Vapour. Mutat. Res. 135:203–209 (1984).
- Erexson, G.L.; Wilmer, J.L.; Steinhagen, W.H.; Kilgerman, A.D.: Induction of Cytogenetic Damage in Rodents after Short-term Inhalation of Benzene. Environ. Mutagen. 8:29–40 (1986).
- 58. McGregor, D.; Ashby, J.: Summary Report on the Performance of the Cell Transformation Assays. In: Evaluation of Short-Term Tests for Carcinogens: Report of the International Program on Chemical Safety Collaborative Study on *In Vitro* Assays, pp. 103–115. J. Ashby, F.J. deSerres, M. Draper, et al., Eds. Elsevier, Amsterdam (1985).
- Post, G.B.; Snyder, R.; Kalf, G.F.: Inhibition of RNA Synthesis and Interleukin-2 Production in Lymphocytes in vitro by Benzene and Its Metabolites, Hydroquinone and p-Benzoquinone. Toxicol. Lett. 29:161–167 (1985).
- Forni, A.M.; Capellini, A.; Pacifico, E.; Vigliani, E.C.: Chromosome Changes and Their Evolution in Subjects with Past Exposure to Benzene. Arch. Environ. Health 23:385–391 (1971).
- Tough, I.M.; Court-Brown, W.M.: Chromosome Aberrations and Exposure to Ambient Benzene. Lancet 1:684 (1965).
- Tough, I.M., Smith, P.G.; Court-Brown, W.M.; Harnden, D.G.: Chromosome Studies on Workers Exposed to Atmospheric Benzene. The Possible Influence of Age. Eur. J. Cancer 6:49–55 (1970).
- Watanabe, T.; Endo, A.; Kato, Y.; et al.: Cytogenetics and Cytokinetics of Cultured Lymphocytes from Benzene-exposed Workers. Int. Arch. Occup. Environ. Health 46:31–41 (1980).
- Killian, D.J.; Daniel, R.L.: Cytogenetic Study of Workers Exposed to Benzene in the Texas Division of Dow Chemical USA, February 29, 1978. OSHA Doc. No. H-059, Exhibit No. 230 X-2. Occupational Safety and Health Administration, Washington, DC (1978).

- Picciano, D.L. Cytogenetic Study of Workers Exposed to Benzene. Environ. Res. 19:33–39 (1979).
- 66. Picciano. D.J.: Monitoring Industrial Populations by Cytogenetics Procedures. In: Proceedings of a Workshop on Methodology for Assessing Reproductive Hazards in the Workplace, pp. 293–306. P.F. Infante and M.S. Legator, Eds. U.S. Government Printing Office, Washington, DC (1980).
- Ding, X.J.; Li, Y.; Ding, Y.: Chromosome Changes in Patients with Chronic Benzene Poisoning. Chinese Med. J. 96:681–685 (1983).
- Sasiadek, M.; Jagielski, J.: Localization of Break-points in Chromosomes of Workers Occupationally Exposed to Benzene. Clinical Genet. 28:462 (1985).
- Sarto, F.; Cominato, I.; Pinton, A.M.; et al.: A Cytogenetic Study on Workers Exposed to Low Concentrations of Benzene. Carcinogenesis 5:827–832 (1984).
- Franz, T.J.: Percutaneous Absorption of Benzene. In: Proceedings of the Symposium: The Toxicology of Petroleum Hydrocarbons, pp. 108–114 H. MacFarland, C. Holdsworth, J. MacGregor, et al., Eds. American Petroleum Institute, Washington, DC (1983).
- Blank, I.H.; McAuliffe, D.J.: Penetration of Benzene Through Human Skin. J. Invest. Dermatol. 85:522–526 (1985).
- Susten, A.S.; Dames, B.L.; Niemeier, R.W.: In vivo Percutaneous Absorption Studies of Volatile Solvents in Hairless Mice. I. Description of a Skin Depot. J. Appl. Toxicol. 6:43–46 (1986).
- Sabourin, P.J.; Chen, B.T.; Lucier, G.; et al.: Effect of Dose on the Absorption and Excretion of [14C]-Benzene Administered Orally or by Inhalation in Rats and Mice. Toxicol. Appl. Pharmacol. 87:325–336 (1987).
- Kalf, G.F.; Post, G.B.; Snyder, R.: Solvent Toxicology: Recent Advances in the Toxicology of Benzene, the Glycol Ethers and Carbon Tetrachloride. Ann. Rev. Pharmacol. Toxicol. 27:399–427 (1987).
- Gonasun, L.M.; Witmer, C.; Kocsis, J.J.; Snyder, R.: Benzene Metabolism in Mouse Liver Microsomes. Toxicol. Appl. Pharmacol. 26:398–406 (1973).
- Medinsky, M.A.; Sabourin, P.J.; Lucier, G.; et al.: A Physiological Model for Simulation of Benzene Metabolism by Rats and Mice. Toxicol. Appl. Pharmacol. 99:193–206 (1989).
- Sawahata, T.; Rickert, D.E.; Greenlee, W.F.; Metabolism of Benzene and Its Metabolites in Bone Marrow. In: Toxicology of the Blood and Bone Marrow, pp. 141–148. R.D. Irons, Ed. Raven, New York (1985).
- Jerina, D.; Daly, J.; Witkop, B.; et al.: Role of Arene Oxide-Oxepin System in the Metabolism of Aromatic Substrates. I. *In vitro* Conversion of Benzene Oxide to a Mercapturic Acid and a Dihydrodiol. Arch. Biochem. Biophys. 128:176–183 (1968).
- Tunek, A.; Plat, K.L.; Pryzybbylski, M.; Oesch, F.: Multistep Metabolic Activation of Benzene. Effect of Superoxide Dismutase on Covalent Binding of Microsomal Macromolecules, and Identification of Glutathione Conjugates Using High Pressure Liquid Chromatography and Field Desorption Mass Spectrometry. Chem. Biol. Interact. 33:1–17 (1980).
- Gaido, K.W.; Wierda, D.: In vitro Effects of Benzene Metabolites on Mouse Bone Marrow Stromal Cells. Toxicol. Appl. Pharmacol. 76:45–55 (1984).
- Greenlee, W.F.; Sun, J.D.; Bus, J.S.: A Proposed Mechanism of Benzene Toxicity: Formation of Reactive Intermediates from Polyphenol Metabolites. Toxicol. Appl. Pharmacol. 59:187–195 (1981).
- Irons, R.D.; Neptun, D.A.; Pfeifer, R.W.: Inhibition of Lymphocyte Transformation and Microtubule Assembly by Quinone Metabolites of Benzene: Evidence for a Common Mechanism. J. Reticuloendothel. Soc. 30:359–372 (1981).
- Irons, R.D.; Neptun, D.A.: Effects of the Principal Hydroxymetabolites of Benzene on Microtubule Polymerization. Arch. Toxicol. 45:297–305 (1980).
- 84. Goldstein, B.D.; et al.: Symposium on Benzene Metabolism, Toxicity and Carcinogenesis. Environ. Health Perspect. 82:3–310 (1989).
- Gosselin, R.E.; Smith, R.P.; Hodge, H.C.: Clinical Toxicology of Commercial Products, 5th ed., pp. II–151. Williams & Wilkins, Baltimore (1984).
- 86. Flury, F.: Moderne gewerbliche vergiftungen in Pharmakologische

- Toxikologische Kinsicht, Arch. Exp. Pathol. Pharmakol. 138:65 (1928). 87. Aksoy, M.; Erdem, S.; DinCol, G.; Leukemia in Shoe-workers Exposed Chronically to Benzene. Blood 4:837-841 (1974).
- 88. Aksoy, M.; Erdem, S.; DinCol, G.; Types of Leukemia in Chronic Benzene Poisoning, A Study in Thirty-four Patients, Acta Haematol, 55.65-72 (1976).
- 89. Aksov, M.: Different Types of Malignancies due to Occupational Exposure to Benzene. A Review of Recent Observations in Turkey. Environ. Res. 23:181-190 (1980).
- 90. Aksoy, M.: Malignancies due to Occupational Exposure to Benzene. Am. J. Ind. Med. 7:395-402 (1985).
- 91. Aksoy, M.: Benzene as a Leukemogenic and Carcinogenic Agent. Am. J. Ind. Med. 8:9-20 (1985).
- 92. Vigliani, E.C.: Leukemia Associated with Benzene Exposure. Ann. N.Y. Acad. Sci. 271:143-151 (1976).
- 93. Infante, P.F.; Rinsky, R.A.; Wagoner, J.K.; Young, R.J.: Leukemia in Benzene Workers. Lancet 2:76-78 (1977).
- 94. Infante, P.F.; White, M.C.; Chu, K.C.: Assessment of Leukemia Mortality Associated with Occupational Exposure to Benzene. Risk Anal. 4:9-13
- 95. Van Raalte, H.G.S.; Grasso, P.; Irvine, D.: Tackling a Very Difficult Problem. Risk Anal. 4:1-2 (1984).
- 96. Rinsky, R.A.; Young, R.J.; Smith, A.B.: Leukemia in Benzene Workers. Am. J. Ind. Med. 2(3):217-245 (1981).
- 97. Rinsky, R.A.; Smith, A.B.; Hornung, R.; et al.: Benzene and Leukemia. An Epidemiologic Risk Assessment, N. Engl. J. Med. 316(17):1044-1050
- 98. Yin, S.N.; Li, G.L.; Tain, F.D.; et al.: Leukemia in Benzene Workers: A Reprospective Cohort Study. Br. J. Ind. Med. 44:124-128 (1987).
- 99. Yin, S.N.; Li, Q.; Tian, F.; et al.: Occupational Exposure to Benzene in China, Br. J. Ind. Med. 44:192-195 (1987).
- 100. Ott, G.M.; Townsend, J.C.; Fishbeck, W.A.; Langner, R.A.: Mortality among Individuals Occupationally Exposed to Benzene. Arch. Environ. Health 33(1):3-10 (1978).
- 101. Occupational Safety and Health Administration: Occupational Exposure to Benzene; Proposed Rule and Notice of Hearing. Fed. Reg. 50:50512-50586 (December 10, 1985).
- 102. Bond, G.G.; McLaren, E.A.; Baldwin, C.L.; Cook, R.R.: An Update of Mortality among Workers Exposed to Benzene. Br. J. Ind. Med. 43(10):685-691 (1986).
- 103. Decoufle, P.; Blattner, W.A.; Blair, A.: Mortality among Chemical Workers Exposed to Benzene and Other Agents. Environ. Res. 30:16-25 (1983).
- 104. Wong, O.: An Industry Wide Mortality Study of Chemical Workers Occupationally Exposed to Benzene. I. General Results. Br. J. Ind. Med. 44(6):365-381 (1987).
- 105. Wong, O.: An Industry Wide Mortality Study of Chemical Workers Occupationally Exposed to Benzene. II. Dose-Response Analysis. Br. J. Ind. Med. 44(6):382-395 (1987).
- 106. Thomas, T.L.; Waxweiler, R.J.; Moure-Eraso, R.; et al.: Mortality Patterns among Workers in Three Texas Oil Refineries. J. Occup. Med. 24:135-141 (1982).

- 107. Wen, C.P.; Tsai, S.P.; McClellan, W.A.; Gibson, R.L.; Long-term Mortality Study of Oil Refinery Workers. I. Mortality of Hourly and Salaried Workers, Am. J. Epidemiol. 118:526-542 (1983).
- 108. Theriault, G.; Goulet, L.; A Mortality Study of Oil Refinery Workers. J. Occup. Med. 21:367-370 (1979).
- 109. Hanis, N.M.: Stavraky, K.M.: Fowler, J.L.: Cancer Mortality in Oil Refinery Workers, J. Occup. Med. 21:167-174 (1979).
- 110. Hanis, N.M.; Holmes, T.M.; Shallenberger, L.J.; Jones, K.E.; Epidemiology Study of Refinery and Chemical Plant Workers. J. Occup. Med. 24:203-212 (1982).
- 111. Schottenfeld, D.; Warshauer, M.E.; Zauber, A.G.: A Prospective of Morbidity and Mortality in Petroleum Industry Employees in the United States. A Preliminary Report. In: Quantification of Occupational Cancer, pp. 247-265. M.A. Schneiderman, Ed. Banbury Report No. 9. Cold Spring Harbor, New York (1981).
- 112. Rushton, L.; Alderson, M.R.: A Case-Control Study to Investigate the Association Between Exposure to Benzene and Deaths from Leukemia in Oil Refinery Workers. Br. J. Cancer 43:77-84 (1981).
- 113. Joyner, R.E.: Leukemia at Shell Wood River and Deer Park Manufacturing Complexes. Letter and Report of Studies to J.D. Millar, Director, NIOSH, dated July 28, 1983. OSHA Docket H-059B, Ex. No. 142-13. Occupational Safety and Health Administration, Washington, DC.
- 114. Tsai, S.P.; Wen, C.P.; Weiss, N.S.; et al.: Retrospective Mortality and Medical Surveillance Studies of Workers in Benzene Areas of Refineries. J. Occup. Med. 25:685-692 (1983).
- 115. International Agency for Research on Cancer: Benzene. IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Humans, Vol. 29, Some Industrial Chemicals and Dyestuffs, pp. 93-148. IARC, Lyon, France (1982).
- 116. Thorpe, J.J.: Epidemiological Survey of Leukemia in Persons Potentially Exposed to Benzene. J. Occup. Med. 16:375-382 (1974).
- 117. Arp, E.W.; Wolf, P.H.; Checkoway, H.: Lymphocytic Leukemia and Exposures to Benzene and Other Solvents in the Rubber Industry. J. Occup. Med. 25:598–602 (1983).
- 118. White, M.C.: Infante, P.F.: Chu, K.C.: A Quantitative Estimate of Leukemia Mortality Associated with Occupational Exposure to Benzene. Risk Anal. 2:195-204 (1982).
- 119. Crump, K.S.; Allen, B.C.; Howe, R.B.; Crocket, P.W.: Time-related Factors in Quantitative Risk Assessment. J. Chronic Dis. 40 (Suppl. 2):1015-1115 (1987).
- 120. Chandler, J.L.R.: Benzene and the One-hit Model. Risk Anal. 4:7-8 (1984).
- 121. Hoel, D.G.; Kaplan, N.L.; Andersen, M.W.: Implication of Nonlinear Kinetics in Risk Estimation in Carcinogenesis. Science 219:1032-1037
- 122. Stommel, P.; Mueller, G.; Stucker, W.; et al.: Determination of S-Phenylmercapturic Acid in the Urine-An Improvement in the Biological Monitoring of Benzene Exposure. Carcinogenesis 10:279-282 (1989).

EPIDEMIOLOGY IN RISK ASSESSMENT FOR REGULATORY POLICY

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"The uncharted galaxies of epidemiology are numerous"

Lilienfeld et al. [11]

1. INTRODUCTION

THE TWENTIETH century has seen the rapid evolution of many new fields concerned with protecting public health. Epidemiology and risk assessment have several of the features common to these new fields, and important differences. Both are needed to make the difficult decisions required in setting standards for levels of toxic agents in the workplace and environment. They differ in their aims, orientation, and time scale.

According to Lilienfeld and Lilienfeld [2], epidemiology is "the study of the distribution of a disease or a physiological condition in human populations and of the factors that influence this distribution" (italics added). By contrast, health risk assessment denotes research and evaluation to characterize the probability of physical harm to humans attributable to a particular agent or group of agents. While the distribution of disease provides the focus for epidemiologic research, concern for adverse effects of specific toxicants drives risk assessment. Moreover, while epidemiologic studies proceed at the glacier-like pace needed to mobilize large staffs of support personnel and to monitor large populations over long periods of time, risk assessment activities acquire the urgency felt by regulators, who must make decisions (including decisions to postpone decisions) today. Most important, while epidemiology is a scientific field that draws upon medicine, demography, and statistics, risk assessment is a hybrid of science and policy that draws not only upon fields such as epidemiology, toxicology, chemistry and engineering, but also upon psychology, politics, economics, law and social justice.

These inherent differences in emphasis, timing, and nature complicate the role played by epidemiology in risk assessment for regulatory policy. In 1985, this role is still largely one of epidemiology's uncharted galaxies. In the sections below, I review the role's history, and the reasons why it will continue to play an essential part in regulatory decision-making. The role has placed epidemiologic findings and epidemiologists at the center of political controversies, and I discuss the positive and negative side effects of this new visibility. Finally, I explore ways to prevent the negative side effects and ways to increase the utility of epidemiologic data for regulatory risk assessment.

11. THE ROLE OF EPIDEMIOLOGY IN RISK ASSESSMENT

Concern about industrially related contaminants in our air, water, and food began gathering momentum shortly before World War II, and accelerated with the publication in 1963 of Rachel Carson's book, The Silent Spring. The spectre she painted of man's

TABLE 1. PARTIAL LIST OF FEDERAL LEGISLATION REGULATING TOXIC SUBSTANCES

| Legislation | Year passed |
|--|-------------|
| Delaney Clause of Food, Drug and Cosmetic Act | 1959 |
| Federal Hazardous Substances Act | 1960 |
| Clean Air Act | 1970 |
| Occupational Safety and Health Act | 1970 |
| Consumer Product Safety Act | 1972 |
| Federal Environmental Pesticide Control Act | 1972 |
| Federal Insecticide, Fungicide and Rodenticide Act | 1972 |
| Safe Drinking Water Act | 1974 |
| Resource Conservation and Recovery Act | 1976 |
| Toxic Substances Control Act | 1976 |
| Clean Water Act | 1977 |

TABLE 2. FEDERAL AGENCIES REGULATING TOXIC SUBSTANCES

| Agency | Year established | | |
|---|------------------|--|--|
| Food and Drug Administration | 1928 | | |
| Environmental Protection Agency | 1970 | | |
| Occupational Safety and Health Administration | 1970 | | |
| Consumer Product Safety Commission | 1972 | | |

TABLE 3. FEDERAL RESEARCH ORGANIZATIONS INVESTIGATING TOXIC SUBSTANCES

| Organization . | Year established |
|---|------------------|
| National Cancer Institute | 1937 |
| National Institute for Environmental Health Sciences | 1969 |
| National Institute for Occupational Safety and Health | · 1971 |
| National Toxicology Program | 1978 |

destruction of the earth with industrial emissions fueled public pressure for a rash of environmental legislation, some of which is listed in Table 1. Tables 2 and 3 show the parallel evolution of federal agencies created by Congress to regulate and control toxic emissions, and of federal research institutes to provide the scientific basis for such regulation. These developments have led many to regard the 1970's as "the decade of the environment". Although motivation for the environmental movement included concern about the adverse effects of contaminants on respiratory function, reproductive outcomes and genetic mutations, the most compelling constituent was public fear that the global destruction predicted by Carson would include an epidemic of chemically induced cancers.

Figure 1 shows temporal trends in the estimated probability that a white male baby born in the U.S. will either develop cancer or die from it. The temporal increase does not reflect the feared epidemic. Rather it reflects the greater proportion of men who will survive to old age when cancer risks are highest, as well as the more accurate diagnoses among the elderly, and the effects of tobacco. Apart from this real increase in cancer incidence and mortality, there is a perceived one due to the openness with which the disease is now

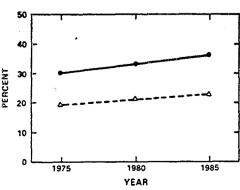


Fig. 1. Trend of lifetime probability for developing (---) or dying (---) of cancer, white male born in the United States. (Source [3]).

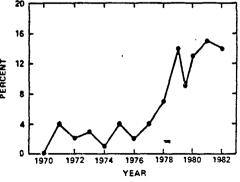


Fig. 2. Proportion of articles published in American Journal of Epidemiology concerned with adverse health effects of physical and chemical agents in the workplace or general environment.

discussed. It is unthinkable today that a U.S. President would undergo furtive oral cancer surgery on a yacht in New York's East River to keep it from his constituents, as did Grover Cleveland in 1893.

The environmental movement of the 1970's has had a direct impact on the substance of epidemiologic studies. Figure 2 shows the increase with time in the proportion of those articles in the American Journal of Epidemiology that are devoted to the adverse effects of physical and chemical agents in the workplace and environment. Although a sizable part of this new research has examined acute and chronic respiratory disorders and reproductive disorders, the largest portion has dealt with environmentally and occupationally induced cancer. That cancer should monopolize a disproportionate share of the research reflects patterns of research funding, which in turn reflect priority patterns of public fear. Many of the examples and much of the discussion in this paper concern the relationship between epidemiology and risk assessment for cancer, although the problems and future prospects apply to other diseases as well.

Estimating risks to health from environmental agents using human data must proceed in the face of formidable obstacles. Most toxic exposures occur chronically at levels that are low, variable, and measured with substantial error. Epidemiologic studies are likely to overlook a large number of small effects associated with such exposures. Data from those occupational studies dealing with high exposures and large effects typically provide limited guidance about risks at low environmental levels, as can be seen by comparing the very high lung cancer death rates of U.S. uranium miners with those of smoking and nonsmoking U.S. veterans, shown in Fig. 3. An individual living in the U.S. today inhales naturally occurring radon gas and its radioactive decay products at an average rate of roughly two-tenths of a WLM per year [6]. (A WLM, the acronym for "working-levelmonth", is a unit of cumulative exposure to α-radiation.) By age 70 he will have inhaled a total of about 14 WLM, a small amount in comparison with totals in excess of 3000 WLM inhaled by U.S. uranium miners before the establishment of a federal standard in 1970. The startling excess of lung cancer among these miners relative to that of other U.S. white males illustrates the difficulty in attempting to use these data to estimate risks from low levels of radiation.

The difficulty is also evident upon examination of the standardized mortality ratios (SMR's) shown in Fig. 4. The SMR's were computed using the entire cohort as the standard, and were normalized so that miners in the lowest exposure category of 0-21 WLM form the referent group. Interest centers on risk among miners in the 22-119 WLM range, because these exposures approximate those experienced by individuals living in areas with very high background radon levels. However, the evidence is equivocal: although the death rate for the 22-119 WLM group is almost twice that of the referent group, the increase is not statistically significant at the 5% level.

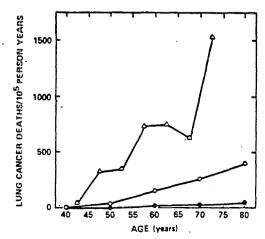


Fig. 3. Age-specific lung cancer mortality rates in U.S. uranium miners (△——△), smoking U.S. veterans (⊙——○) and non-smoking U.S. veterans (⊕——●). (Source [4, 5].)

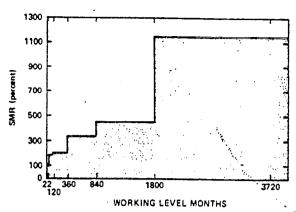


Fig. 4. Standardized mortality ratios (SMRs) for lung cancer by working-level-months (WLM) of cumulative exposure in United States uranium miners. SMRs were normalized to 100% for exposure category 0-21 WLM. (Source [4]).

Monitoring populations for disease is time-consuming, expensive, and vulnerable to serious bias. One must worry that comparisons between exposed and unexposed populations are not confounded by differences in smoking and other determinants of health, nor biased by differences in subjective assessments of disease. Such worries are aggravated in studies of environmentally induced disease, because the effects are likely to be small and the danger of reporting bias great.

These obstacles do not vitiate the strengths of epidemiology in risk assessment for regulatory policy. As noted by Doll in the context of policy-setting for the prevention of cancer [7], human observations continue to make several essential contributions to risk assessment. In the paragraphs below I list some of the reasons why human data are needed for regulatory decisions.

First, they are needed to detect unsuspected hazards that have not emerged from laboratory tests. Animal experiments are still imperfect tools for detecting human cancer, largely because of the great variability across species in response to chemicals, and our lack of understanding about the causes of this variability. The International Agency for Research on Cancer has determined that there is sufficient evidence from human observations, but limited, inadequate, or nonexistent evidence from animal experiments, to classify as carcinogens the chemicals or chemical processes listed in Table 4. The fact that most of these chemicals have tested positive in one or more of the short-term in vitro or in vivo tests now in use, reflects not the sensitivity of the test battery but rather the intense scrutiny the chemicals have received, relative to those for which no human data are available. Moreover, the tests are not specific; one or more of them have been positive for a vast number of chemicals occurring naturally in the foods we eat and the products we use. Thus laboratory tests do not yet provide a reliable screen for human carcinogens, and they are of limited or no utility for many other diseases or conditions associated with environmental exposures. Human data will continue to be needed, despite the obvious desirability of discovering health hazards before human exposure to them.

Second, human data are needed to estimate exposure levels producing the highest additional risk that is socially acceptable. Just as laboratory tests provide imperfect screens

TABLE 4. CHEMICALS OR INDUSTRIAL PROCESSES WITH SUFFICIENT® EVIDENCE FOR CARCINOGENICITY IN HUMANS BUT NOT IN EXPERIMENTAL ANIMALS!

Arsenic and certain arsenic compounds
Manufacture of auramine
Benzene
N,N-bis(2-cholorethyl)-2-naphthylamine (chlornaphazine)
Undergroud mining of hematite
Manufacture of isopropyl alcohol (strong acid process)
Mustard gas
Nickel refining

^{*}As defined by the International Agency for Research on Cancer [8]. †Source: [8].

Table 5. Estimated human bladder cancer risks (cancers/10° population) for lifetime saccharin ingestion of 0.12 g/day*

| | L | ow dose extrapo | lation method | |
|-----------------------------------|------------|-----------------|---------------|--------|
| Interspecies extrapolation method | Single-hit | Multistage | Multihit | Probit |
| Body surface area | 1200 | 5 | 0.001 | 450 |
| mg/kg/day | 210 | _ | 0.001 | 21 |
| mg/kg/lifetime | 5200 | _ | 0.001 | 4200 |

^{*}Extrapolated from Rat Bladder Tumor Data. Source [9].

TABLE 6. RISK OF BLADDER CANCER AMONG USERS OF ARTIFICIAL SWEETENERS RELATIVE TO RISK AMONG MONUSERS (ESTIMATED FROM CASE-CONTROL STUDIES)

| Authors | Males | Females |
|------------------------|-------|---------|
| Hoover et al. [10] | 0.99 | 1.00 |
| Kessler and Clark [11] | 0.97 | 1.01 |

for potential toxicants, so also are they extremely limited tools for obtaining quantitative estimates of risk. Table 5 shows that estimates of human bladder cancer risk associated with saccharin, derived from a single positive experiment in laboratory rats, can differ by as much as six orders of magnitude, depending on the assumptions used to extrapolate across species and dose level. By contrast, the consistent lack of association found in six case-control studies of bladder cancer (see Table 6 for a sample) provide an upper bound on the actual level of human risk. Of course, neither human nor laboratory data can prove that a substance is harmless, but consistent negative findings in humans provide reassurance about the probable magnitude of the hazard.

Third, human data are needed to check inferences about a putative cause for a disease by_monitoring the effect of its removal. Such checks require time, due to the long lag between exposure onset (or termination) and disease occurrence that is characteristic of many chronic diseases. For example, we can only now begin to monitor the effects on U.S. lung cancer rates of reductions in tar and nicotine content of cigarettes and in cigarette use since the 1950's. Figure 5 shows a modest but clear downward trend with year of birth in age-specific lung cancer death rates among young U.S. white males. Each successive birth cohort contains fewer men who started smoking, and among those who did, a higher proportion who smoked low tar cigarettes.

Finally, human data are needed to provide a sense of perspective about the magnitude of various hazards to health, in order to set priorities for the expenditure of public and

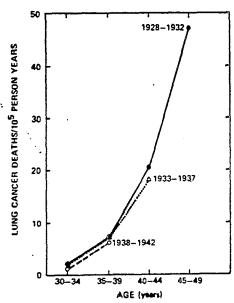


Fig. 5. Age-specific lung cancer mortality rates in United States white male cohorts. (Source [12].)

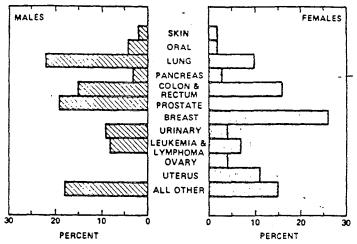


Fig. 6. Estimated percentage of all incident cancers occurring by site of origin in United States males or females in 1985, excluding nonmelanoma skin cancer and carcinoma in situ. (Source [13].)

private health resources so as to avoid spending disproportionate sums of money on minor hazards, while neglecting major ones. Figure 6 shows estimates of the percentage of all cancers diagnosed in the U.S. in 1985 occurring among the major sites, for men and women separately. Among men, cancers of the lung, large intestine and prostate account for about 56% of all new cancers (and 57% of all cancer deaths). Among women, cancers of the lung, large intestine and breast comprise 52% of all new cancers (and 51% of all cancer deaths). Table 7 shows that occupational and environmental factors do not play an appreciable role in the etiology of these major causes of morbidity and mortality, except for lung cancer. Moreover, the contribution to lung cancer is dwarfed by that of tobacco, which has been estimated to account for 91 and 79% of lung cancer deaths among U.S. men and women, respectively [14]. (The sum of the percentages for males exceeds 100% because of the multifactorial etiology of lung cancer.) To date, we have made slow progress in preventing cancers of the breast, prostate, and large intestine, which are more likely to

Table 7. Estimated percentages of the major site-specific cancers attributable to occupational and environmental factors*

| | Males | Females |
|------------------|-------|---------|
| Lung | 15 | 5 |
| Colon and rectum | 2 | 1 |
| Prostate | < i | _ |
| Breast | _ | 0 |

TABLE 8. BIOLOGICAL MARKERS FOR ENVIRONMENTAL EXPOSURES

*Source [14].

| Marker | Specimen | Methodology Refs |
|---|--|--|
| Chromosome aberrations (breaks, rearrangements, sister chromatid exchanges) | Blood lymphocytes, erythrocytes in bone marrow | Autoradiography, phytohemagglutinin stimulation of lymphocytes [33, 34] |
| Micronuclei | Erythrocytes in bone marrow | Microscopic examination [35] |
| Covalent binding to DNA | Blood lymphocytes, tissue explants | Radioactive labeling: immunoassays: indirect immunofluorescence microscopy [36] |
| Covalent binding to cellular proteins | Hemoglobin | Chromatography [37] |
| Cellular atypia | Sputum, cervical epithelium | Microscopic examination [38] |
| Mutagens | Urine, feces, cervicul secretions, breast fluids | Ames salmonella test [39] |
| Sperm abnormalities | Semen | [40] |

kill us than are the pesticides we use to attack the insects in our homes. Such a perspective could help to assuage fear of cancer from environmental toxicants, and to direct the expenditure of public funds toward more cost-effective priorities.

III. THE IMPACT OF RISK ASSESSMENT ON EPIDEMIOLOGY

Clearly, epidemiologic observations continue to play an indispensable role in risk assessment for regulatory policy, and conversely, increasingly many epidemiologic studies are devoted to occupationally and environmentally induced disease. Increased public awareness of environmental issues and the need for risk assessment has brought epidemiology into courts, into homes on the evening news, and into leisure reading in the Sunday newspaper supplement. Thanks to such publicity, epidemiology is no longer an arcane word for an esoteric specialty. The need for epidemiology in risk assessment has brought employment opportunities and interesting scientific problems to epidemiologists. But it has also produced negative effects.

Problems arise because risk assessment is not a science, but rather a complex and often subtle fusion of facts and values. The problems are aggravated by the prevailing misconception that risk assessment for toxic substances is (or should be) entirely objective and scientific. This misconception is illustrated by the statement of the Office of Science and Technology Policy, Executive Office of the President, that toxic substance regulation consists of two stages: Stage I (risk assessment) uses empirical data and scientific judgement to characterize human exposure and risk; Stage II (policy) uses social and political action to decide regulatory action [5]. This separatist view is echoed by the National Academy of Sciences Committee on the Institutional Means for Assessment of Risks to Public Health, which reported:

"We recommend that regulatory agencies take steps to establish and maintain a clear conceptual distinction between assessment of risks and consideration of the risk management alternatives; that is, the scientific findings and policy judgements embodied in risk assessments should be explicitly distinguished from the political, economic, and technical considerations that influence the design and choice of regulatory strategies" [16].

While it is useful to call attention to the desirability of such a distinction, I believe that in practice it is an unrealistic and unattainable goal. Values enter toxic risk assessment in many covert ways. They determine the quantity and quality of information obtained about a chemical, influence explicit and implicit assumptions used to analyze data, affect the way data are interpreted, and influence the weights used to combine disparate sets of data (see Ref. [17] for examples). This mix of science and policy can have undesirable effects on the quality of epidemiologic research by compromising the design, conduct, analysis, and interpretation of studies.

Adverse effects on the design and conduct of studies can occur in several ways. Political pressures to find quick answers to difficult questions have prompted poorly designed and hastily conducted investigations of possible danger from air pollutants and toxic wastes (e.g. Ref. [18]). The findings of such studies have been heavily criticized and the resulting controversies do not help the image of the field. Sometimes political pressures completely prevent a study. For example, an attempted county-wide investigation of the reproductive effects of aerial malathion spraying for the Mediterranean fruit fly was aborted because the hospital with the largest proportion of births declined to participate, due to the inflammatory political climate at the time [19]. Conversely, political pressures have initiated unwarranted studies virtually doomed to be inconclusive because of low, poorly documented exposures and lack of focus on specific disease entities. In the words of Doll [7]:

"An epidemiological perspective starts not with the 10,000 chemicals that pollute a particular area, but with the 10,000 deaths that occur in that area each

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year, and seeks to determine the major causes of those actual deaths. Such a perspective is much more likely to overlook a large number of small effects of various chemicals than laboratory science might be, but it is much less likely to overlook the chief determinants of current mortality rates_and trends, especially if these are not simple direct effects of individual chemicals on molecular DNA".

Quality control and data analysis also are complicated by the political climate surrounding many studies of environmentally induced disease. The possibility of subjective reporting bias is increased, causing greater need for exposure and outcome validation [20]. For subjective disease assessments such as miscarriages and asthma attacks, there is need for difficult and expensive validation of negative outcomes among both exposed and unexposed populations.

Political pressures have their largest impact on the interpretation of epidemiologic data. Pressure to provide "bottom lines" produces quantitative risk estimates with spurious precision, numbers that, out of context, take on a life of their own. Such numbers are overinterpreted by laymen who expect a study to produce unequivocal answers, and when it does not, who criticize epidemiology for failing to achieve aims that go beyond available resources or methodologic capabilities.

Perhaps the most troubling impact of risk assessment activities concerns their side-effects for the epidemiologist. He has joined the ranks of psychiatrists, statisticians, and clinicians who take the stand as expert witnesseses in multimillion dollar lawsuits. While this activity helps keep bread on the table, one worries about the conflict between the one-sidedness of such an advocacy position and all of one's training to strive for a balanced perspective in weighing the strengths and limitations of a data set and placing it in the broader context of other data. Apart from the monetary inducements to take a unilateral view, there can also be pressures from peers and employers. Espousal of unpopular views may cost an epidemiologist invitations to conferences, permission by an employer to attend conferences [21], favorable reviews of papers, or even a job [22]. These hazards of course are not quite unique to the epidemiologist, but are shared by all those in the environmental health sciences whose work impinges on risk assessment for regulatory policy.

Equally worrisome is the tendency for political and philosophical differences to masquerade as scientific disputes. By now we have become inured to the familiar spectacle of government and industry epidemiologists aligning themselves in predictable camps in hassles over such issues as the incidence of brain tumors in the petrochemical industry [23], the fraction of U.S. cancer deaths attributable to occupational exposures [24], and the toxic importance of lead in automobile exhaust relative to that of lead in paint [25]. A second manifestation of this masquerade is the overkill in critiques of completed studies whose results have undesirable implications for the interests of one or another faction in a regulatory issue. While constructive peer review is a useful process, critiques that exaggerate a study's flaws and overlook its strengths for the purpose of discrediting its conclusions are counterproductive and a poor use of resources [26].

One can look back in history for more subtle and therefore perhaps more disturbing examples of how values influence scientific conclusions. Samuel George Morton was a 19th century self-styled "objective empiricist" who used his extensive collection of human skulls to study racial differences in cranial capacity, a putative marker for intelligence. His findings supported contemporary caucasian beliefs: whites above indians, blacks at the bottom. Stephen Jay Gould reanalyzed Morton's meticulously recorded raw data, and found a fabric of apparently unconscious manipulations in the form of errors, miscalculations and omissions, all in favor of white supremacy [27]. Gould notes that unconscious or dimly perceived finagling is probably endemic in science, since scientists are human beings rooted in political and cultural contexts. This example serves as a sobering reminder that reporting and interpreting one's data can require soul-searching, ruthless honesty, and courage.

IV. THE FUTURE

It seems likely that public concern for environmental issues will not abate within this century, that public and corporate funds will continue to support research to monitor and evaluate environmental and occupational hazards to health, and that epidemiology will continue to play a critical role in this endeavor. It is therefore worthwhile to ask how regulators and epidemiologists can counteract the negative impacts of the political pressures endemic to regulation, and how epidemiologists and epidemiologic studies can provide guidance and support for the overall thrust of regulatory policy, as well as for the difficult decisions faced by regulators.

One antidote for the negative side effects of politicization on epidemiologic research is awareness of the hybrid nature of risk assessment activities. We need to recognize that a neat separation of regulatory policy into matters of fact and value is illusionary, and to sensitize ourselves to value judgements when they occur. They will and must occur, because setting standards for hazards at work and in the environment is a social and political process.

It is possible to abate political pressures by allocating sufficient funds, time and qualified personnel to the careful conduct of well designed studies, and by incorporating into the studies the advice of experts chosen to represent the concerns of all sides in sensitive issues. Recent investigations of pregnancy outcomes among women whose drinking water had been contaminated by a chemical leak from an underground tank at an electronics company provide a model for achieving such abatement. These investigations were conducted by the California Department of Health Services with the cooperation of the Santa Clara County Department of Health [32]. Before beginning the studies, the principal investigators formed an advisory committee of epidemiologists representing the interests of industry and of the citizens. The committee had a voice in the design, the data collection, the analyses and the interpretation of findings. The resulting consensus report provided a voice of reason that cooled many tempers in the heated political dispute surrounding the issues.

Epidemiologists can make their data more useful to regulators in several ways. A first step is good documentation. Clear, thorough and complete recording of the details and data that led to a study's conclusions are needed by regulatory scientists who must use the conclusions to formulate policy statements for public approval. The completeness of recording is important. Serfling [28] has decried the filtering of data and relevant research results that seem to contradict strongly held views about exposure effect, citing some occupational studies as examples. In 1981 the Interagency Regulatory Liaison Group published guidelines for documentation of epidemiologic studies [29, 30]. There now seems to be a consensus that these guidelines have been helpful in improving the clarity and completeness of study reports, and that they have not been the unwelcome intrusion of government agencies into epidemiologic turf feared by some.

Apart from the regulatory scientists' need for documentation of technical details and raw data, there is the layman's need for clear, nontechnical documentation of a study's conclusions, with particular emphasis on the degree of precision and sources of uncertainty associated with the conclusions. The policy decisions for which epidemiologic evidence is needed concern the public, and the public must make those decisions. Informed decisions by laymen require exposition of the major findings of a study, as well as the sources and nature of uncertainty about the findings in clear English without the use of esoteric jargon.

A second step to enhance the utility of epidemiologic data involves more evenhandedness among epidemiologists about the strengths and weaknesses of a study, and less dredging for flaws with intent to discredit. It is imperative that scientists attempt to form a consensus about the interpretation of data, so that the courts are not forced to resolve technical scientific issues they are ill-equipped to handle. David L. Bazelon, Senior Court Judge of the U.S. Court of Appeals for the District of Columbia Court, complained that scientists cannot agree about the reliability of data, and that "... they disagree even more about the inferences to be drawn from the facts. Often, they can tell us only of 'the risk of risk'.... Courts must not be expected to resolve such questions. What judge knows enough to understand issues on the frontiers of nuclear physics, toxicology and other specialities informing health and safety regulations?" [31].

While it may be naive to think that epidemiologists can reach a consensus about uncertain data when millions of dollars and lives are at stake, there is no feasible alternative but to try to do so. The reproductive studies in Santa Clara County, and others like them, provide a paradigm for achieving such a consensus.

A third step to increase the utility of epidemiologic observations for risk assessment is aggressive monitoring of occupationally exposed populations. This is largely a job for industrial epidemiologists and occupational physicians, who should keep computerized. annually updated and linkable medical, job and smoking histories for all current (and to the extent feasible, former) employees. As noted by Doll [7], this monitoring makes sense from the industrial point of view, since most such studies would reveal no excess risk, and the accumulated negative human evidence, coupled with estimates of exposure levels for various agents, would be useful in resisting overzealous regulation. The monitoring also makes sense from the worker's point of view, because real hazards would be detected earlier than they otherwise might be. Finally, it makes sense for the public who would learn that prolonged exposure to quantified levels of many of the agents feared harmful have not produced observable human hazards.

The most promising developments in the monitoring of exposed populations involve the use of biological exposure markers in blood, tissue, urine, feces, hair or nail samples. Table 8 lists several of the markers detectable and quantifiable in human specimens. Such markers have the potential to document exposure levels, identify and quantify unusual susceptibility to environmental toxicants, detect precursors of injury or organ dysfunction, and provide etiologically supportive biological links between exposure and disease. Epidemiologic studies are needed to determine how well they correlate with exposure, and with preclinical or clinical manifestations of disease. They are also needed to determine the marker's reproducibility and persistence over time. Industrially exposed cohorts and cohorts of patients undergoing chemotherapy are ideal populations for such studies.

CONCLUSIONS

Epidemiology continues to play an indispensable role in risk assessment for regulatory purposes. Human data are needed to detect hazards missed by laboratory experiments, estimate exposure levels producing the highest socially acceptable risks, monitor changes in disease rates after the removal of putative causal agents, and provide a perspective for cost-effective allocation of public health resources.

Epidemiologists can make their data even more useful for risk assessment by providing clear and complete documentation for other scientists, and jargon-free documentation for those not versed in epidemiologic methods. Equally important is data interpretation with more balance and less factiousness. All of these objectives would be facilitated by the dialogue resulting from symposia, and from postdoctoral fellowships and visiting appointments allowing academic, regulatory and industrial epidemiologists to visit one another's worksites.

Occupationally exposed populations should be monitored for exposure levels, morbidity and mortality. Biological markers in human specimens promise to afford useful indices for exposures and for unusual susceptibility to exposures. There is need for work to correlate these markers with exposure history and with disease, and to establish their reproducibility, variability and persistence over time.

Risk assessment is both a political and a scientific process, and politicization will continue to complicate the conduct of epidemiologic research on the effects of environmental toxicants. Some restraint of political pressures can be achieved by allocating the funds and time for studies of high quality, with ongoing input from epidemiologists representing all interested parties.

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REFERENCES

- 1. Lilienfeld DE, Lilienfeld AM: Epidemiology 101: The new frontier. Int J Epidemiol 7: 377-380, 1978
- Lilienfeld AM, Lilienfeld DE: Foundations of Epidemiology, 2nd edn. New York: Oxford University Press, 1980
- Seidman H, Mushinski MH, Gelb SK, Silverburg E: Probability of eventually developing or dying of cancer—United States, 1985. CA-A 35: 36-56, 1985
- Halpern J, Whittemore AS: Issues in analyzing cohort data: application to lung cancer mortality in uranium miners. J Chron Dis In press
- Kahn HA: The Dorn study of smoking and mortality among US veterans: report on 8! years of observations. In Epidemiologic Approaches to the Study of Cancer and Other Chronic Diseases, Haenszel W (Ed.). NCI Monogr No. 19, 1966. pp. 1-126
- George AC, Breslin AJ: The distribution of ambient radon and radon daughters in residential buildings in the New Jersey-New York area. In The Natural Radiation Environment III, Gessel TF, Lowder WM (Eds). Washington. DC: Technical Information Center-U.S. Department of Energy, 1980
- 7. Doll R: Relevance of epidemiology to policies for the prevention of cancer. J Occup Med 23: 601-609, 1981
- Chemicals and Industrial Processes Associated with Cancer in Humans. IARC Monogr. Vols 1-20. Lyon, France
- 9. Federal Register 45(15), 22 January, 1980. p. 5200
- Hoover RN, Strasser PH: Artificial sweetness and human bladder cancer—preliminary results. Lancet 8173: 873-840, 1980
- 11. Kessler II, Clark JP: Saccharin, cyclamate and human bladder. JAMA 240: 349-355, 1978
- 12. Vital Statistics of the US 1960-1979, Vol. II-Mortality, Part A. Hyattsville, Md: National Center for Health Statistics
- 13. Silverberg E: Cancer statistics. CA-A 35: 19-35, 1985
- 14. Doll R. Peto R: The causes of cancer: quantitative estimates of avoidable risks of cancer in the Unites States toolay. J Natl Cancer Inst 66: 1191-1308, 1981
- Calkins DR, Dixon RL, Gerber CR, Zarin D, Omenn GS: Identification, characterization and control of
 potential human carcinogens: A framework for federal decision-making. J Natl Cancer Inst 64: 169-176,
 1980
- Committee on the Institutional Means for Assessment of Risks to Public Health. Risk Assessment in the Federal Government: Managing the Process, Washington D.C.: National Academy Press, 1983
- Whittemore AS: Facts and values in risk analysis for environmental toxicants. Risk Anal 3: 23-34, 1983
- Kolata GB: Love Canal: False alarm caused by botched study. Science 208: 1239–1282, 1980
- Petittii D: Studying potential reproductive hazards. In Environmental Epidemiology: Risk Assessment, Prentice RL, Whittemore AS (Eds). Philadelphia, Penn. SIAM Publications. 1982. pp. 49-62
- Roht LH, Vernon SW, Weir FW, Pier SM, Sullivan P, Reed LJ: Community exposure to hazardous waste disposal sites: Assessing reporting bias. Am J Epidemiol 122: 418-433, 1985
- 21. Sun M: EPA said to bar official from Meeting. Science 214: 629, 1981
- 22. Sun M: A firing over formaldehyde. Science 213: 630-631, 1981
- 23. Lewin R: Government/industry brain tumor risk. Science 210: 996-997, 1980
- Occupational Safety and Health Administration: Estimates of the Fraction of Cancer in the United States Related to Occupational Factors, filed in Congressional Record (September 15, 1978)
- 25. Marshall E: The politics of lead. Science 216: 496, 1982
 - Soskolne CL: Epidemiologic research, interest groups and the review process. J Publ Health Policy 6: 173-184, 1985
 - 27. Gould SJ: Morton's ranking of races by cranial capacity. Science 200: 503-509, 1978
 - Serfling TD: Filtering information about occupation, smoking and disease. J Chron Dis 37: 227-230, 1984
 - 29. Verhalen RD: Guidelines for documentation of epidemiologic studies. Am J Epidemiol 114: 609-613, 1981
 - 30. Labarthe DR: Commentary: The Interagency Regulatory Liaison Group "Guidelines for Documentation of Epidemiological Studies". Am J Epidemiol 114: 614-618, 1981
 - 31. Bazelon DL: Science, technology and the court. Science 208: 661, 1980.
 - 32. Pregnancy Outcomes in Santa Clara County 1980–1982. Reports of two epidemiologic studies. Berkeley, CA:

 California State Department of Health Services, 1985
 - Raposa T: Sister chromatid exchange studies for monitoring DNA damage and repair capacity after cytostatics in vitro and in lymphocytes of leukaemic patients under cytostatic therapy. Mutat Res 57: 241-251, 1978
 - Evans HJ, O'Riordan ML: Human peripheral blood lymphocytes for the analysis of chromosome aberrations in mutagen tests. Mutat Res 31: 135-148. 1975
 - Högstedt B, Gullberg B, Mark-Vandel E, Mitelman F, Skerfving S: Micronuclei and chromosome aberrations in bone marrow cells and lymphocytes of humans exposed to petroleum vapors. Heriditas 94: 179-187, 1981
 - Perera FP, Weinstein IB. Molecular epidemiology and carcinogen-DNA adduct detection: new approaches
 to studies of human cancer causation. J Chron Dis 35: 581-600, 1982

- 37. Osterman-Golkar S, Ehrenberg L: Dosimetry of electophilic compounds by means of hemoglobin alkylation. Ann Rev Public Health 4: 397-402, 1983
- Holmquist ND. Detection of urinary cancer with urinalysis sediment. J Urol 123: 188-189, 1980
 Hollstein M, McCann J, Angelosanto FA, Nichols WW: short term tests for carcinogens and mutagens Mutat Res 65, 133-226, 1979
- 40. Dougherty RC, Whitaker MJ, Tang S-Y et al. Sperm density and toxic substances: a potential key to environmental health hazards. In Environmental Health Chemistry, McKinney JD (Ed.), Ann Arbor, Mich. Ann Arbor Science Publishers, 1981, pp. 263-278

Use of Animal & Other Data As Predictors of Human Risk

Crouch

Risk Analysis in Environmental and Occupational Health

Use of animal and other data as predictors of human risk

Edmund Crouch

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1 Elackground Information

It is useful to bear in mind a few sobering facts about total populations at risk, and the normal total risk of death and of dying of cancer. For the U.S., the total population is about 240 million, while the annual number of deaths is about 2 million per year and the annual number of cancer deaths is about 400 thousand. These figures imply an annual average total risk of death of about 10^{-2} (1 percent per year), and a lifetime risk of cancer of about 0.2 (20 percent, or $200,000 \times 10^{-6}$), estimates you can obtain simply by dividing one figure by another.

Of course, simply dividing one by another is not a particularly accurate way of computing such estimates — one should do the correct thing and take the age structure of the population into account, and the variation of risks with age, and so on. But even when you do precisely that, the average lifetime risk of cancer comes out to be about 20 to 25 percent. We can expect this figure to get higher as the expectation of life increases, and as other causes of death are eliminated (assuming — pessimistically — that most cancers cannot be eliminated). It is mainly the increase in expectation of life which has made cancer such a prominent cause of death in the (historically) recent past, because cancers tend to be diseases of old age.

For many cancers it is found that the death rate varies as a power of age:-

where the exponent n is in the range 4 to 11. For such cancers, this pattern seems to hold over the age range from about 30 to 65. At lower ages the rates tend to be very small but almost independent of age (and the cancers may be completely different diseases in youngsters), while at higher ages the reported death rates are lower than would be predicted by this sort of formula - and in some cases the reported death rates are actually lower for old enough groups. It is unclear whether these reductions in death rates in the elderly are real, or are simply due to a difference in the accuracy of diagnosis and reporting. It is also possible that the reduction in reported death rates is real, but is due to the winnowing out of the population of those who are susceptible to these particular cancers, leaving a core of more resistant individuals.

The major exceptions to the power law variation of death rate with age are the cancers which are known to be hormonally dependent (e.g. breast cancer), or are highly curable (skin cancers), or in which the natural progression is altered by intervention (e.g. a high proportion of women have had hysterectomies by age 65, so that they cannot be at risk of uterine cancers thereafter).

With this age variation of risk of cancer understood, we can now oversimplify again and quote a lifetime average annual risk for cancer, obtained simply by dividing the lifetime risk by an average lifetime of about 70 years. This give an average annual risk of about $2-3 \times 10^3$. Notice that we

are here averaging over a lifetime — the figure is not meant to imply that the risk is the same in each year of life — we have just seen that it varies drastically with age.

When discussing the risks of carcinogens, the same caveats have to be borne in mind. We usually attempt to estimate a lifetime risk but may express this, for comparison purposes, as an annual average risk. For an individual exposed continuously to a carcinogen, we would expect that the risk of cancer increases with age in a fashion similar to the risk of other (naturally occurring) cancers.

There is another reason also for quoting an annual average risk obtained by averaging over a lifetime. When estimating risks of carcinogens, one is often interested in the response of a population to exposure to the carcinogen. In this case, one should strictly (if it were possible) estimate what the effects at all future times would be on individuals of different ages at the times of exposure. The effects at all future times on the whole population would then be an average over the effects on all the individuals in the population (who were of different ages at the times of exposure.

Thus, to obtain an estimate of the effects on a population, one implicitly performs an average over the age groups present in the population. If the population were stationary (and if certain other conditions were fulfilled) this average would be the same as an average over a lifetime. This explains the usefulness of a lifetime average, since one may argue that the differences between population and lifetime averages are small compared with other uncertainties inherent in all the procedures we will describe later.

The preceding discussion must be considered only a heuristic argument for accepting a lifetime average as being useful. In practice, people will be exposed at different ages, and for varying periods, to different amounts of carcinogens. All these differences (and many more besides) will affect the probability of carcinogenesis for each of them.

2 Known Human Carcinogens

There is now good evidence that human exposure to certain materials can, under certain conditions, increase the rate of human cancer. The evidence comes from various types of epidemiological investigation (discussed in other talks in this course). In all cases, exposures to these materials has been high, compared with population exposures, and the population exposed has been small compared with the total U.S. population. The resultant risks to those exposed has been substantial.

The following table indicates a few of these materials, and the types of cancer which have been caused in humans by exposure to them.

| Material/Action | Site or type of tumor | Material/Action | Site or type of tumor |
|---|-----------------------------|--|-----------------------------|
| 4-Aminobiphenyl Aurarnine manufacture Benzidine Chlornaphazine Cyclophosphamide 2-Naphthylamine | Bladder | Arsenic (compounds) Asbestos BCME CCME Chromium (VI compounds) Mustard gas Nickel refining | Lung |
| Arsenic PUVA Soots, Tars, Mineral oils | Skin | Benzene Myleran Chlormabucil Melphalan | Leukemia |
| DES (In utero) | Vagina | Vinyl Chloride | Liver |

The "natural" rates for these cancers, expressed in terms of lifetime risk and annual average risk, are shown in the following table.

| Site or type of tumor | Lifetime Risk | Annual Average | | | | | | | |
|--------------------------------|--------------------------|----------------------|--|--|--|--|--|--|--|
| | (In ABSENCE of exposure) | | | | | | | | |
| Bladder | 5 × 10 ⁻³ | 7 × 10 ⁻⁵ | | | | | | | |
| Lung (Pop ⁿ . ave.) | 4 × 10 ⁻² | 6 × 10 ⁻⁴ | | | | | | | |
| Skin (deaths) | 3 × 10 ⁻³ | 4 × 10 ⁻⁵ | | | | | | | |
| Liver | 1 × 10 ⁻³ | 2 × 10 ⁻⁵ | | | | | | | |
| Vagina | 7 × 10 ⁻³ | 9 × 10 ⁻⁵ | | | | | | | |
| Leukemia | 8 × 10 ⁻³ | 1 × 10 ⁻⁴ | | | | | | | |

Typically, in epidemiological studies, a relative risk of more than 2 is required in order to detect any effect. Thus the (epidemiologically) discoverable population average human risks are > 10⁻⁵ per year, or 10⁻³ per lifetime, and probably much larger. For the small subgroups of the population usually available for study, the observable risks are generally much larger. For example, in the groups of workers exposed to vinyl chloride, the relative risk for angiosarcoma of the liver was huge, mainly because angiosarcoma of the liver is such a rare disease. Had vinyl chloride caused a more common tumor of the liver, it is quite likely that the association with vinyl chloride exposure would have been missed. In animals, vinyl chloride induces other tumors at a greater rate than angiosarcomas (although it also induces them), and current quantitative risk assessments are based on these other tumor types.

3 Target Risks. The Necessity of Extrapolation.

When considering the size of acceptable risks to the public at large, the usual targets are much smaller than the discoverable risks discussed above. Typically they will be less than 10⁻⁶ per year. Note that the EPA and the FDA set targets of order 10⁻⁶ to 10⁻⁴ per lifetime, that is, of order 10⁻⁸ to 10⁻⁶ per year.

It must also be borne in mind that there are a large number of materials which are of potential interest. The Chemical Abstracts Service (CAS) has now given names to well over six million distinct chemicals which have been mentioned in scientific literature, and there have been various estimates of the number (around 50,000) of chemicals in general commercial use.

With such numbers, it should be immediately apparent that there are just too many time, money and logistical constraints to directly detecting any adverse effects from such a plethora of materials to which humans may be exposed. Notice that a risk of 10⁻⁶ per lifetime corresponds to a rate of about 3 per year in the whole U.S. population. Thus, even if the whole U.S. population were exposed to some material causing a risk of death of 10⁻⁶ per lifetime, the resulting deaths would be statistically indistinguishable in the usual two million deaths per year (unless there were something extremely unusual about the deaths).

Extrapolation is therefore essential in order to estimate the sizes of risks, and hence be in a position to demand that risks be reduced to the levels mentioned. The fundamental observation on which such extrapolation is based is that:

HUMAN CARCINOGEN ⇒ ANIMAL CARCINOGEN

In other words, every known material which has been shown to be a human carcinogen is also known to cause tumors in animals *under suitable conditions*. This observation is not very useful in itself, but what is done in order to allow risk assessments is to assume its converse:

ANIMAL CARCINOGEN ⇒ HUMAN CARCINOGEN

and to work from here. This assumption is not unreasonable, in view of what is known about carcinogenesis — although it is something which can be argued about in specific cases. It is also well to be aware of the phrase emphasized — "under suitable conditions". While it may be true that animal carcinogens are indeed human carcinogens, the conditions of exposure of humans may typically be very different from the conditions under which the material is carcinogenic to animals. It may be that under the conditions of human exposure, the material is not carcinogenic in animals or humans.

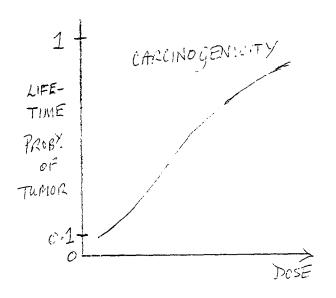
4 The Nature of Carcinogenesis.

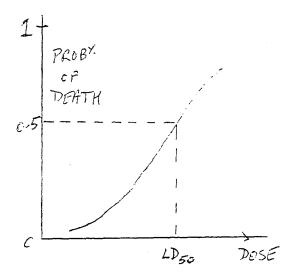
In what follows, it is useful to keep in mind some information about the process of carcinogenesis. This information has been derived from studies of humans and animals, and from experiments performed *in vivo* or *in vitro*. It is based partly on experimental studies, and partly on theoretical ideas suggested by those studies.

- Cancers arise from one (or more) individual cell(s) which have gone "out of control" in some way - the cell becomes immortal, with no limit on the number of cell divisions, and the usual constraints on cell division no longer apply. A cell may pass through several stages before reaching this state.
- The underlying cause of such behavior is probably some effect(s) on the genetic material of the cell, but the exact mechanism(s) is (are) unknown.
- The occurrence of such events appears to be a random process at some level. One cannot tell which individual cell or animal or person will be affected. Hence we talk about the PROBABILITIES of cancer the chance that some event will occur.
- When we feed materials to experimental animals, the probability for cancer depend on various factors which can be manipulated. For example, the probability varies with:

The total AMOUNT of material (the total dose)
The AGE at which dosing takes place
The RATE OF APPLICATION, or the time over which dosing continues
OTHER FACTORS (some known — stress, dietary factors, ..., others unknown)

We therefore expect, and in practice observe, DOSE-RESPONSE curves. Such dose-response curves are fundamental in extrapolating risks to humans. I like to draw an analogy to the similar problem of extrapolation which arises for acute toxicity — in both



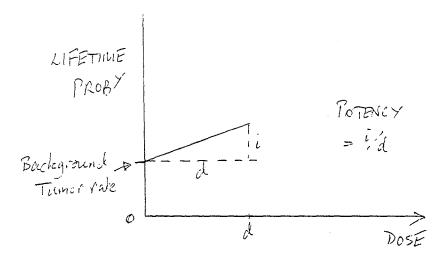


- Evidently there will be some AGE STRUCTURE to the probabilities of cancer. As mentioned, for many cancers in humans the death rate from cancers increases with a power of age. In experimental studies involving long term feeding of rodents, the same sort of age structure is found for the incidence of tumors. A "LIFETIME" probability thus depends on when you measure it — the usual practice is to assume a "standard" lifetime of ~70 years for humans and ~2 years for rodents.
- At high enough doses (i.e. at high RESPONSES) one sees interactions between different materials in both animal experiments and in human data (e.g. smoking and alcohol consumption, smoking and radon exposure, smoking and asbestos exposure). The effect of such interactions is to make the effect of two or more materials different from the sum of the effects of the materials individually (at the same doses).
- It is not possible to make direct measurements of what happens at low doses (i.e. at LOW RESPONSES). In this context, low dose means a dose at which the response probability is < 0.1 usually, and < 0.01 certainly. Any attempt at studying lower doses runs up against problems of logistics, cost and the background cancer rate.
- The shape of dose-response curves assumed for the low dose regions are thus based

Theoretical ideas Prejudice Guesswork

For performing risk assessments for human safety purposes, there is naturally a prejudice to be conservative.

It is generally agreed that assuming LINEARITY between dose and response (for our discussion, this means the lifetime probability of a cancer) at low enough doses is CONSERVATIVE. This assumption is made in a theoretical way — it is assumed that the true relationship between dose and response lies, at low enough doses, entirely below (or at worst on) a linear curve joining the response at zero dose (background) with the response at some higher (but still low) dose.



Typically, the background rate is of order 10⁻⁴ to 10⁻¹, and we are interested in excesses over the background of order 10⁻⁶ to 10⁻⁴, so this diagram is not to scale. It is useful to define the POTENCY of a carcinogen as the ratio of excess lifetime probability of cancer to the dose causing that excess (at low enough doses). On the diagram, this is the ratio i/d. The potency is thus the slope of the dose-response curve at low enough dose, and we have the basic equation:

EXCESS RISK = POTENCY × DOSE

There is reasonable evidence that some mechanisms of carcinogenesis result in a THRESHOLD — i.e. that there is some (threshold) dose below which the excess incidence of cancer is much lower than would be predicted by a linear extrapolation from doses above the threshold, and possibly that the excess incidence of cancer is literally zero below such a threshold (excess, here, means excess over the background occurrence of cancer). Some of the evidence for such mechanisms comes from observation of the dose-response curves in experimental situations — the experiments on saccharin provide a good example. However, there is still the possibility that a linear mechanism may still operate at low enough doses, and so any human risk assessment has to take that possibility into account.

5 The Standard Animal Test.

The requirements for a "standard" animal test are quite severe. The animals involved have to be as similar to humans as possible — in metabolism, in being omnivorous, in their sensitivity to chemicals, for example — yet as different as possible in their life span and cost of upkeep (so that we can get results in a reasonable time at a reasonable cost). In practice, there is little option but to use standard laboratory animals. The usual choices are rodents — rats and mice; with occasional tests being performed on golden hamsters or guinea pigs. Other animals (e.g. gerbils) have been proposed, but for now the experience built up in handling laboratory rodents is a strong incentive for continuing their use despite certain known disadvantages. Any change would now have to be done gradually, and with much cross checking with previous results.

It is now standard to require tests to be performed in at least two species (practically always rats and mice) and on both sexes, in case one or the other species or sex is peculiarly resistant to the material under test. A compromise has to be made over the number of animals to test. It would be desirable to have as many as logistically possible, to increase the statistical sensitivity of the experiment; but as few as possible to minimize the costs of testing (since there is always another material to test). The current recommendation is for at least 50 per group of similarly treated animals.

There is a similar trade-off between costs and the number of dose levels to test in a given experiment. The current recommendation is to have at least three, preferably four or more, dose groups — an undosed group (the control group), a group tested at the maximum tolerated dose (MTD) of the material under test, and the third group tested at some intermediate dose (usually 1/4 to 1/2 of the MTD).

The MTD of a material is roughly defined to be as much as possible, but not enough to kill off the animals early or to cause too large other overt effects (like loss of weight). The reason for using it in these experiments is to increase the sensitivity, on the basis that giving more of something is more likely to produce a response if any response if going to happen at all. The sensitivity has to be as high as possible, since the observable responses are of the order 10⁻¹ (10%) while the risks of interest are of order 10⁻⁶ (100,000 times smaller). The alternative way of increasing sensitivity is to increase the number of animals tested (within reason), but this only increases sensitivity in proportion to the square root of the numbers tested, while increasing the dose gives an increase in sensitivity roughly proportional to the dose. Clearly the latter is most cost effective.

Even with such a minimum design, there are:

3 dose groups \times 2 sexes \times 2 species \times 50 animals per group

giving a minimum of 600 animals per experiment. All the animals have to be carefully housed (under standard conditions), cared for, and individually tracked throughout their two year lifetime. They are then sacrificed and a large number of their tissues examined individually. None of this comes cheap — the cost of such an experiment is unlikely to be less than \$200,000, and may run above \$1,000,000.

It should be noted that the type of experiment detailed here is the minimum considered necessary to answer a YES/NO question: Is this material carcinogenic under the conditions of this standard bioassay? The experimental design and analyses performed are designed to be unlikely to answer YES if there is no carcinogenic action present (so that the experiments have low alpha error), but they can easily answer NO even in the presence of carcinogenic action. This sort of test is exactly what is required, of course, if one is interested in identifying materials which are surely carcinogens; in order to study their mechanism of action for example — one doesn't want to accidentally end up with a material with no carcinogenic action.

I would submit, however, that for the purposes of protection of public health, the questions asked of the tests are entirely the wrong way round. For protecting public health, one should surely ask not whether this material is almost surely a carcinogen, but how strong a carcinogen it could be, given the results of the experiment. The fact that the same sort of analysis is applied now as in the past is perhaps a combination of accident and inertia, but one has to admit that, for the most part, the methodology has been largely successful so far.

6 Raw Results - and what to do with them.

Having spent 2 years performing the experiment described above, what output do we get? When the animals are sacrificed, they are dissected and a whole list of tissues examined, both macroscopically and microscopically. All lesions, whether related to cancer or not, are noted down and usually (nowadays) recorded in some sort of computer database. The pathologists performing the examinations usually use some sort of standardized nomenclature for what they observe — for example, the National Toxicology Program uses a modified version of the Systematized Nomenclature for Pathology (SNOP). Other information about individual animals is also recorded — such information as where they came from, which cages they were kept in, when they died (e.g. if they died naturally, or were sacrificed at the end of the experiment, or sacrificed earlier because they clearly would not survive), and so forth.

The outcome is that for each animal, we have a list of the lesions affecting them when they died. An example of a condensed listing of just the cancer-related lesions is appended. From such listings, we can perform various analyses and statistical tests to see whether the rate of cancer was increased at any site or for any type of cancer.

The simplest sort of analysis can be performed if all the animals survived for the whole length of the experiment — and in practice the same sort of analysis is performed provided a reasonable fraction survived that long and provided there were not too many early deaths. In that case, we can simply list the dose groups and the numbers of animals with tumors compared with the total number of animals examined; for example:

| Dose | Number with Tumor | Number Examined |
|------------------|-------------------------|--------------------|
| 0 (control) | 10 | 50 |
| $0.5 \times MTD$ | 25 | 50 |
| MTD | 30 | 50 |

However, things are not usually this simple. Similar results are available for

- Many different sites
- Many different tumor types
- Combinations of these

as will be seen in the examples to follow. To determine whether the rate of cancer has been increased involves comparing the proportion with tumor in the control group with the proportion with tumor in the dosed groups, and deciding whether there is a significant increase in any dosed group(s). The choice of which sites and/or types of tumors to combine before performing such statistical tests can be difficult. Generally, various grades of tumors (nodules, adenomas, carcinomas) may be combined for any given site.

In addition to the simple numbers of animals with tumor, there is additional information available which may be used in more complicated cases. The date of death of each animal is recorded, and may be taken into account in time-adjusted analyses of tumor incidence and in the life-table tests mentioned on the appended material.

For risk assessment purposes, it is necessary to make various assumptions about the behavior of animals in experiments like these. For example, it is assumed that:

- Animals are affected independently (a tumor in one animal has no effect on any other animal).
- Animals are equally likely to be affected
- Each animal receives the same dose and so forth.

It is assurned that cage effects, littermate effects, the effects of heating, lighting, stress etc. are either not present, or are randomized among all the animals in such a way that there will be no effect on the final analysis.

With such assumptions, the probability of an animal having a tumor is related to the dose by some sort of dose-response relationship, so that at any given dose this probability can be computed. The observed results, a number of animals with tumor out of a larger number examined, is then a binomial sample with this probability. In practice, we don't know what the dose-response relationship is - we wish to estimate it from the results. But we assume that we know the SHAPE of the dose-response relationship (specified by a mathematical formula), so that all that is required is to estimate some PARAMETERS in the mathematical formula.

For example, the E.P.A. uses a dose-response relationship of the form:

$$p = 1 - \exp\left\{-\left(q_0 + q_1 d + q_2 d^2 + \dots + q_{k-1} d^{k-1}\right)\right\}$$

when there are k doses in an experiment, where p is the lifetime probability of tumor at dose d. It is usual to use a maximum likelihood technique to estimate the various parameters q_0 , q_1 , q_2 , ... q_{k-1} , given the observed numbers of animals with tumors and the numbers of animals examined at each dose.

In cases where there is appreciable early mortality in the experiment, so that the observed numbers of animals with tumors are likely to be underestimates of what would have been observed at the end of a perfect experiment, one can make modifications to the dose response relationship, just as one can make life-table adjustments to standard statistical tests. One technique used is to modify the dose response curve to explicitly include length of life, using the idea that probability of tumor is likely to increase with a power of age (see page 2):

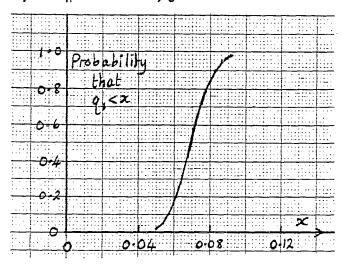
$$p = 1 - \exp\left\{-\left(q_0 + q_1 d + q_2 d^2 + \dots + q_{k-1} d^{k-1}\right) (t/L)^n\right\}$$

where t is the age at death, and L is a standard lifetime. The parameter n can either be fixed at some reasonable value (in the range 2 to 11), or estimated from the experimental results. This technique suffers from the same limitations as the usual modifications to the standard statistical

tests — one has to introduce additional assumptions in order to apply it. In this case, one has to decide whether the tumors were a cause of death, or simply incidental.

An alternative technique used when there is early mortality is to estimate the age dependence directly from the data, using a (so-called) non-parametric technique. This approach has been used to assemble a large database of comparable analyses of animal bioassays.

This methodology has taken the raw results of the animal experiment, and summarized them in the form of a dose-response curve with known parameters. It is also possible to estimate how uncertain one is about a given parameter, using the same maximum likelihood techniques used to obtain point estimates of them - indeed, one can plot the uncertainty distribution for any of the parameters. For example, for the parameter q_1 (which will turn out to be the one of interest), we can plot the probability that q_1 lies below any given value:

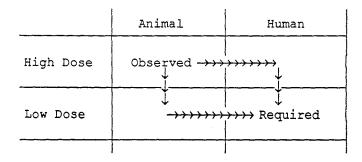


In particular, we can find that value q_1^* such that there is 95% probability that $q_1 < q_1^*$.

However, it is important to note that the uncertainty distribution so plotted contains only the uncertainty due to the numerical size of the experiment — the uncertainty that arises because we used a small number of animals, instead of an infinite number. It does not include the uncertainties which must be present because of the shakiness of all our assumptions — i.e. the major uncertainties.

7 The Two Major Extrapolations

The assumptions made so far have allowed us to parametrize an animal dose-response relationship, obtaining values for the parameters which are presumably reasonably appropriate for high doses. Strictly speaking, this parametrization of the dose-response curve only enables us to estimate the results we would expect to see at high doses in animals -the dose-response relationship can only be relied on to interpolate between high doses and perhaps to extrapolate a short distance outside the experimental range of doses. The problem now is to perform two extrapolations - from animals to humans, and from high dose to low dose:



LOGICALLY there are two distinct routes to follow in this extrapolation, since there are logically two distinct dose-response curves involved (see below). One can extrapolate from high dose to low dose using the ANIMAL dose-response curve, and then extrapolate to humans (dashed lines), or extrapolate to humans at high doses and then use a HUMAN dose-response curve to extrapolate to low doses.

We have seen how to estimate the parameters of the (high dose region of) the animal dose-response curve. In practice, the same curve (with the same parameters) is used to extrapolate to low doses, by building into the mathematical structure of the dose-response curve all our assumptions about low dose behavior.

How is this relevant for estimating human risk? Consider a generalized situation in which we wish to estimate the response (R) of humans to some dose (D) of material, when there is a response (r) in some experimental system at dose (d). Notice that nothing implies that r, R measure the same sort of response - they could be completely different (r could be acute toxicity to the lung of a mouse, R could be skin rashes in humans). Similarly, the dose measures d, D may be completely different. In the case immediately at hand, r is the lifetime probability of tumor in animals, and d is a dose as measured in the animal experiment. There are other cases of practical importance however - r might be some measure of response (such as number of

revertants per culture dish) in a mutagenesis bioassay, with d the dose applied to each culture dish.

| System —> | Arbitrary | Arbitrary Animal bioassay example | | | | | | | |
|---------------------|--------------------|---|--------------------|--|--|--|--|--|--|
| Response | r | p (lifetime prob ^y . of tumor | R | | | | | | |
| Dose measure | d | d (as used in expt.) | D | | | | | | |
| Dose-response curve | r = f(d; a,b,c,,t) | $p = 1-exp\{-(q_0+q_1d+)\}$ | R = F(D; A,B,C,,t) | | | | | | |

What is required is some connection between the parameters a,b,c,... of the dose-response relationship in the experimental system and the parameters A,B,C,... of the human dose-response relationship. These parameters presumably include those mentioned in Section 6, and I have explicitly included age amongst them. Given such a connection, the extrapolation to humans of the results in the animal studies is perfectly straightforward. The problem lies in finding the connection.

Once such a connection is found (by whatever means) we have the methodology for the two extrapolations required. Notice the difference between what is done in the two distinct pathways of extrapolation mentioned above:

In the first, the shape of the dose-response curves are examined, and it is decided how they may be (separately) extrapolated to low doses. Then some relationship is postulated between the parameters of the dose-response curves at low doses (it has to be postulated, since nothing can be **measured** at such low doses). One potential advantage of this approach is that the animal dose-response curve could be measured, in principle and by heroic experimentation, down to lower response rates than usual (and this has been done in some cases) - allowing greater confidence in this extrapolation to low dose.

In the second, some relation between the parameters of the dose-response curves is obtained at high doses (and this may be done experimentally, in principle, since at high doses the responses are measurable). Then it is decided how the human dose-response curve should be extrapolated to low doses. The advantage here is the possibility of direct comparison between species, albeit at high dose.

The difference between these two logically distinct routes of extrapolation might be important in some circumstances. For cancer risk assessment based on animal carcinogenesis bioassays, however, the distinction is glossed over (one might even say, ignored), by the practice of assuming the same (or very similar) mathematical form for the dose-response curve in both humans and animals (or more generally, in all species), and interpreting the parameters in the same way for both compared species.

In the general case, however, what is required is some sort of relationship between the parameters of the dose-response curves:

Animal

Human

r = f(d; a,b,c...t)

R = F(D; A,B,C...T)

We need to be able to derive the parameters A,B,C... from the values a,b,c which can be estimated from experiments, and then use the human dose-response curve to extrapolate to low doses.

The practical approach is to seek parametrizations of the dose-response curve which result in the derivation of A,B,C... being **simple** given a,b,c... Consider the case of acute toxicity, for example. It is found that the shape of the dose-response curve for acute toxicity, in which the response is death, is very similar for a large number of toxins and for many different species. There is, in this case, a threshold-type dose-response curve which can be nicely parametrized by two values: the dose at which 50% of the animals tested can be expected to die (under suitable conditions), and the slope of the dose-response curve at this dose. The first parameter is known as the LD₅₀ (the second has no special name).

Why is this parametrization useful? If the LD_{50} s of various materials in one species are plotted against the LD_{50} s of the same materials in another species, one finds approximate proportionality between them (the plot is a straight line). This can be expressed as, for example,

LD_{so}(rabbit) is proportional to LD_{so}(mouse).

Even more remarkable, it turns out (at least, it did for a particular group of chemicals) that if the dose is measured in a suitable way, as (amount)/(surface area of animal), then **approximately** we have numerical equality in the values of LD_{50} :

 $LD_{50}(rabbit) = LD_{50}(mouse) = LD_{50}(other species)$

It is this approximate equality which explains the utility of the LD_{50} . The other parameter used in defining the dose-response curve, the slope of the curve at the LD_{50} , is not involved in this

relationship. Had we chosen some other method of parametrization, it is quite possible the required interspecies relationship between parameters would be much more complicated.

8 Interspecies Comparison - Constant Relative Potency

What is sought is a simple relationship between the parameters of dose-response relationships in different species. When it is assumed that the dose-response relationship includes a term linear in dose, there is a simple measure of the strength of a carcinogen - the carcinogenic potency (the slope of the dose-response curve at low dose). The simplest hypothesis is that for different species, the ratio of carcinogenic potencies is constant for different materials, so that if material A is twice as potent a carcinogen as material B in species 1, it will also be twice as potent as material A in species 2. This is the idea of constant relative potency, as applied to carcinogenesis, and it underlies the standard approaches to estimating human risks from animals.

There is even some data which supports this idea! There have been several hundred bioassays performed simultaneously on rats and mice, and when the results of these are parametrized using a close-response relationship which includes a linear term, we can estimate the potency in two species for each material tested. Plotting the potency measured in rats versus the potency measured in mice for each material then gives the figure shown (page 24). Notice that each measurement is uncertain to greater or lesser degree, due to the relatively small numbers of animals tested. If the idea of constant relative potency were exactly correct, these points would all lie on a straight line on the figure - or at least, all would lie sufficiently close to such a line that the measurement uncertainty bars on each point would encompass the line. From the figures, one can see that:

- (1) On average, potency in one species is proportional to potency in the other species.
- There is a large scatter of the points around the lines of exact proportionality a scatter bigger than would be expected from the measurement errors alone.

A similar comparison can be attempted between the potencies measured in animal experiments, and those observed in humans (page 24). These cases have arisen in the past where humans have been exposed to materials before they were known to be carcinogenic. We can make use of other's misfortune to estimate how potent each such material is in humans, and compare with estimates obtained for mice and rats in laboratory experiments. In this case, the uncertainties are so large that little can be quantitatively stated, although qualitatively the idea of constant relative potency does not seem to be disproved. A more recent and much more thorough study of comparisons between humans and animals has been carried out for the E.P.A. by Allen, Crump & Shipp and the qualitative results are similar (page 25) — although Allen et al. do not quantitatively evaluate the correlation.

9 Interspecies comparisons - practical and theoretical

The measure of carcinogenic potency introduced above was roughly defined as the ratio of (excess tumor probability)/(dose), at low enough dose. For the E.P.A. model usually used in risk assessments:

$$p = 1 - \exp \left\{ -(q_0 + q_1 d + q_2 d^2 + \dots + q_{k-1} d^{k-1}) \right\}$$

the corresponding measure is q_1 . When this dose-response relationship is used with real data, it is usual to use an "upper 95% confidence limit" estimate q_1^* of q_1 as the measure of potency, since such an estimate is always non-zero (while, for example, the maximum likelihood estimate is often zero). The "upper 95% confidence limit" is with respect to the numerical uncertainties of the experiment only, and so this estimate of potency is in no sense an upper limit with respect to all the other uncertainties involved.

To compare humans with animals, the approach taken is to postulate a similar dose-response relationship in both cases:

Animal Human
$$p = 1 - \exp\{-(Q_0 + Q_1 d + ...)\}$$

$$p = 1 - \exp\{-(Q_0 + Q_1 D + ...)\}$$

and then the constant relative potency hypothesis suggests that Q_1 is proportional to q_1 , and so one hopes to say that:

$$Q_1 = constant \times q_1^*$$
 or at least $Q_1 < constant \times q_1^*$

where the constant depends only on which animals species is used. We expect the constant to be different for different animal species - it will presumably depend on how we measure dose, on the relative lifespans of animal and human, on relative metabolic rates, and a whole host of other factors. With enough experiments, we could measure the constant in this relationship - at least in comparing animal with animal, rather than human with animal - and (in theory) empirically determine how it varies with these factors. The figures mentioned above suggest that the constant is not completely constant, but that there is some sort of random uncertainty built in (or at least, an uncertainty that we can treat as random), amounting to an average factor of about 5.

If we are very lucky, it may be possible to find some way of measuring dose so that the constant in the above relationship is numerically equal to 1, so that the potency is equal in different species (up to the uncertainties) - just as it was possible to find such a measure in the case of the LD₅₀.

It has now become standard practice for risk assessments to <u>assume</u> that the constant is exactly unity if the dose is measured as a (daily average amount)/(surface area of animal), by analogy with the LD_{50} case. The graphs shown on page 24 actually suggest that it would be better to assume an average factor of unity, with an uncertainty factor of about 5 to 7, when the dose is measured as a (daily average amount)/(bodyweight of animal). This assumption will probably change some time in the future when better information is available, or when an alternative theoretical framework suggests a better idea.

10 An example - 1,2 Dibromoethane

As an example of the procedures usually adopted, let us look at the case of 1,2-Dibromoethane. What follows is by now means complete, but it indicates the sort of analysis which has to be performed. This example is confined to analyzing just one result out of many, in a single bioassay (of about 5). In practice, it is essential to look at all the results.

The bioassay I have chosen was an inhalation bioassay in the National Toxicology Program series. A summary of the study design for rats (the design for mice is very similar) is:

| | Initial | Time on stu | dy (weeks) | | | | | | | |
|------------|-------------------|-------------------------|------------|----------|--|--|--|--|--|--|
| | number of animals | ppm (6 hr/d, 5 d/wk) | Exposed | Observed | | | | | | |
| Male Rats | | | | | | | | | | |
| Control | 50 | . 0 | 0 | 104–106 | | | | | | |
| Low dose | 50 | 10 | 103 | 1 | | | | | | |
| High close | 50 | 40 | 88 | 0-1 | | | | | | |
| | | Female Rats | | | | | | | | |
| Control | 50 | 0 | 1 | 104–106 | | | | | | |
| Low dose | 50 | 10 | 103 | 1 | | | | | | |
| High dose | 50 | 40 | 91 | 0-1 | | | | | | |

We will look only at the results in female rats. First, their survival was not as good as might be desired (see graph below) in such an experiment, but the early mortality was probably largely due to the cancers appearing in the study, so it is acceptable - we can use (at least initially) the

simplest analysis based on "end-of-life" data, without having to worry too much about the age dependence (this should always be backed up by further analysis, of course).

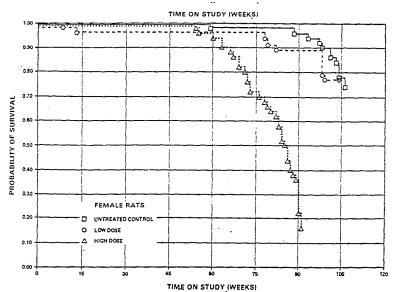


Figure 2. Survival Curves for Rats Exposed to Air Containing 1, 2-Dibromoethana

Tumors were found in many tissues. A summary of those tissues where more than 5% of the animals in any group were found with tumors is (for female rats):

| | Control | Low | High |
|---|---------|-------|-------|
| Subcutaneous tissue: fibroma | 0/50 | 0/50 | 3/50 |
| Subcutaneous tissue: fibroma or fibrosarcoma | 0/50 | 0/50 | 4/50 |
| Nasal Cavity: Carcinoma, NOS | 0/50 | 0/50 | 25/50 |
| Nasal Cavity: Squamous cell carcinoma | 1/50 | 1/50 | 5/50 |
| Nasal Cavity: Adenoma, NOS | 0/50 | 11/50 | 3/50 |
| Nasal Cavity: Adenocarcinoma, NOS | 0/50 | 20/50 | 29/50 |
| Nasal Cavity: Adenomatous Polyp, NOS | 0/50 | 5/50 | 5/50 |
| Nasal Cavity: Papillary Adenoma | 0/50 | 3/50 | 0/50 |
| Nasal Cavity: Adenoma, NOS; Carcinoma, NOS; Adenocarcinoma, NOS; Papillary Adenoma Adenomatous polyp, NOS; and Squamous cell Carcinoma | 1/50 | 34/50 | 43/50 |
| Lung: Alveolar/Bronchiolar Carcinoma | 0/50 | 0/48 | 4/47 |
| Lung: Alveolar/Bronchiolar Carcinoma or Adenoma | 0/50 | 0/48 | 5/47 |
| Hematopoietic System: All leukemias | 6/50 | 7/50 | 1/50 |

| Hematopoietic System: Monocytic leukemia | 6/50 | 5/50 | 1/50 |
|--|-------|-------|-------|
| Circulatory System: Hemangiosarcoma | 0/50 | 0/50 | 5/50 |
| Circulatory System: Hemangiosarcoma or Hemangiosarcoma, invasive | 0/50 | 0/50 | 5/50 |
| Liver: Neoplastic nodule | 2/50 | 0/49 | 3/48 |
| Liver: Hepatocellular carcinoma | 0/50 | 1/49 | 3/48 |
| Liver: Neoplastic nodule or Hepatocellular carcinoma | 2/50 | 1/49 | 5/48 |
| Pituitary: Adenoma, NOS | 1/50 | 18/49 | 4/45 |
| Pituitary: Chromophobe adenoma | 20/50 | 0/49 | 0/45 |
| Adrenal: Pheochromocytoma | 3/50 | 1/49 | 0/47 |
| Thyroid: C-cell Carcinoma | 1/49 | 3/48 | 1/45 |
| Mammary Gland: Adenocarcinoma, NOS | 1/50 | 0/50 | 4/50 |
| Mammary Gland: Fibroadenoma | 4/50 | 29/50 | 24/50 |
| | | | |

Notice especially the various groupings which are employed - this is a matter of judgement. It is clear that the major effect is in the nasal cavity, but observe also the effect on fibroadenomas in the mammary gland, and the **negative** trend seen in the pituitary. Such negative trends are generally **ignored**. Further analysis, taking account of the age at death, might show such a negative trend is an artifact caused by the early deaths in the dosed groups, but here the result in the low dose group suggests that the effect is real.

Using the combined results in the nasal cavity, we fit the E.P.A. multistage model and find best estimates of:

$$q_0 = 2.699 \times 10^{-2}$$
; $q_1 = 6.876 \times 10^{-2}$; $q_2 = 0$;

and obtain an upper confidence limit for q_1 of $q_1^* = 8.6 \times 10^2$, in each case using as doses the values 0, 10 and 40 ppm from the experimental design. In fact, the earlier figure of a distribution of values for q_1 is taken from this example - you can read the probability of q_1 being less than any given value from that figure. What this means is that the linear term in the relation between risk and dose is probably less than 8.6×10^2 per ppm (under the conditions of the experiment).

Now what do we do with this estimate? That depends on the application, but we will assume that we wish to make a "UNIT RISK" estimate for humans from it — that is, estimate an upper bound lifetime risk to a human exposed to 1 μ g/m³ of dibromoethane for life.

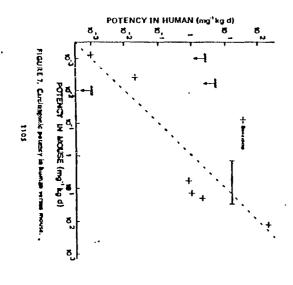
There are several extrapolations required. First, the animals were dosed for a lifetime, but not continuously. Correcting for continuous exposure introduces a factor of $7/5 \times 24/6$ (for days/week and hours/day) — but notice the subtle assumptions being made here, that it is **average** exposure that matters (and not peak exposure, for example).

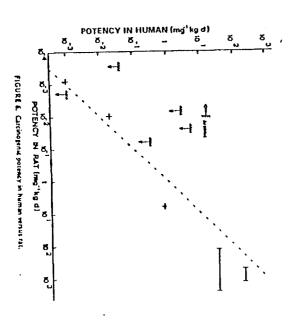
Now we estimate that a female rat will suffer and increased lifetime risk of less than $7/5 \times 24/6 \times 8.6 \times 10^{-2} = 0.48$ per ppm in the air (we assume that we are talking about such low doses that the excess risk is small). 1 ppm for 1,2-dibromoethane corresponds to about 7.6 mg/m3 (one would estimate a little higher from the perfect gas laws), or 7600 μ g/m3, so that the increased lifetime risk to a female rat exposed continuously to 1 μ g/m3 is less than about $0.48/7600 = 6.3 \times 10^{-5}$.

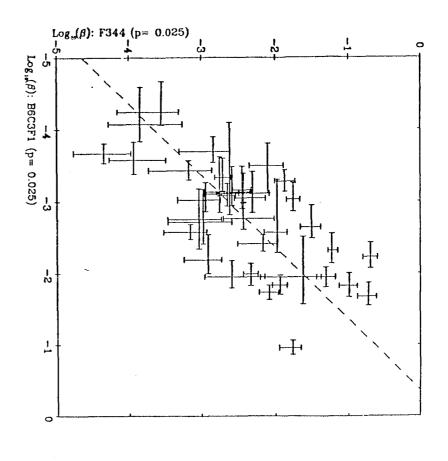
What about humans? We saw before that the assumption made was that humans are just as sensitive as animals - i.e. they suffer equal lifetime risks - if exposed at doses which are equal on an (amount)/(surface area) basis. Now it turns out that, approximately, equal concentrations in air lead to exposures which are equivalent on this basis, provided the species under consideration absorb about the same amount from the air they breathe. Thus the extrapolation to humans is simple in this case -one simply takes the same value for humans - a "UNIT RISK" of less than about 6.3×10^{-5} (i.e. this is our overestimate for the lifetime risk from continuous exposure to 1 μ g/m3 of dibromoethane in the air).

It may be desired to estimate from this the effect on humans of ingestion of dibromoethane. In this case there are actually other bioassays in which dibromoethane was fed to animals under various conditions, but suppose that we have to make some estimate from the inhalation data. The "standard" human inhales, on average, about 20 m³ of air per day, and so inhales about 20 μ g/day of contaminant from air contaminated with 1 μ g/m³. If we assume that 100% of this contaminant is absorbed, the human's daily dose is 20 μ g/day, or about 20/70 μ g/kg-day (as a fraction of bodyweight), or 2.9 × 10⁴ mg/kg-day in the conventional units used. This results in a risk of about 6.3 × 10⁻⁵, as detailed above, so that the potency is just the ratio of these — 0.22 (mg/kg-day)⁻¹.

These short outline calculations have made several assumptions which require examination in any particular case. We have not looked at all the bioassay results, so one cannot expect that the numbers obtained here will correspond with what anybody else, who has done a more thorough job, will obtain — they are placed here in order to show in outline what is done. In practice, one has to decide that the tumor site and type combinations are appropriate for combination in the animal species. That these tumors are relevant end points for estimating the probable effects on humans. That the route of administration, and method of administration are reasonable to produce results that may be extrapolated to humans. And a myriad of other details which have only been lightly touched upon, or completely omitted, in this sketch.









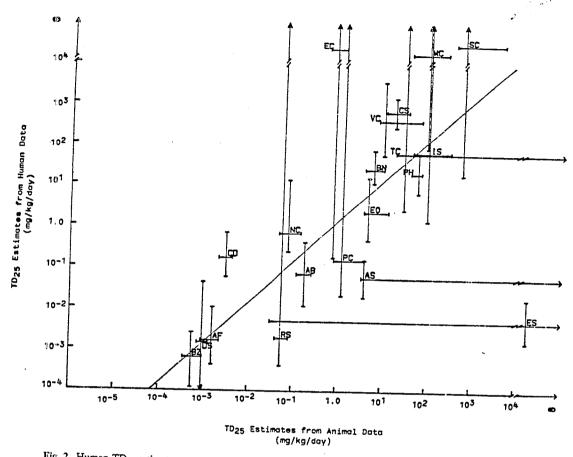


Fig. 2. Human TD_{25} estimates versus animal TD_{25} estimates obtained from base case (analysis 0); log-log plot.

TABLE E3. ANALYSIS OF PRIMARY TUMORS IN MALE MICE (Continued)

| | Vehicle Control | 500 mg/kg | 1,000 mg/kg |
|---|--------------------|--------------|----------------|
| | | | |
| Circulatory System: Hemangiosarcoma Overall Rates (a) | 4/50 (8%) | 3/49 (6%) | 1/50 (2%) |
| Adjusted Rates (b) | 10.1% | 8.8% | , |
| * - | * * | · · | 2.6% |
| Terminal Rates (c) | 3/38 (8%) | 2/33 (6%) | 1/39 (3%) |
| Life Table Tests (d) | P=0.130N | P=0.559N | P=0.169N |
| Incidental Tumor Tests (d) | P=0.097N | P=0.408N | P=0.176N |
| Cochran-Armitage Trend Test (d) | P=0.134N | | |
| Fisher Exact Tests | | P=0.512N | P=0.181N |
| Circulatory System: Hemangioma or He | _ | | |
| Overall Rates (a) | 4/50 (8%) | 4/49 (8%) | 1/50 (2%) |
| Adjusted Rates (b) | 10.1% | 11.8% | 2.6% |
| Terminal Rates (c) | 3/38 (8%) | 3/33 (9%) | 1/39 (3%) |
| Life Table Tests (d) | P=0.142N | P=0.579 | P=0.169N |
| Incidental Tumor Tests (d) | P=0.110N | P=0.573N | P=0.176N |
| Cochran-Armitage Trend Test (d) | P=0.147N | | |
| Fisher Exact Tests | | P=0.631 | P=0.181N |
| Liver: Adenoma | | | |
| Overall Rates (a) | 0/50 (0%) | 5:49 (10%) | 13, 50 (26%) |
| Adjusted Rates (b) | 0.0% | 13.0% | 33.3% |
| Terminal Rates (c) | 0/38 (0%) | 3,33 (9%) | 13/39 (33%) |
| Life Table Tests (d) | P<0.001 | P=0.030 | P<0.001 |
| Incidental Tumor Tests (d) | P<0.001 | P=0.023 | P<0.001 |
| Cochran-Armitage Trend Test (d) | P<0.001 | . 0.025 | . (0.001 |
| Fisher Exact Tests | . 40.001 | P=0.027 | P<0.001 |
| Liver: Carcinoma | | | |
| Overall Rates (a) | 10, 50 (20%) | 14, 49 (29%) | 12 50 (24%) |
| Adjusted Rates (h) | 24.3% | 35.9% | 25.8% |
| Terminal Rates (c) | 7,38 (18%) | 9 33 (27%) | 5 39 (13%) |
| Life Table Tests (d) | P=0.427 | P=0.183 | P=0.463 |
| , , , | P=0.536 | P=0.379 | P=0.548N |
| Incidental Tumor Tests (d) | P=0.363 | 1 -0.379 | 1 -0.246.3 |
| Cochran-Armitage Trend Test (d) Fisher Exact Tests | F=0.303 | P=0.224 | P=0.405 |
| | | r=0.224 | 1-0.403 |
| Liver: Adenoma or Carcinoma | 10 50 (20%) | 18 49 (37%) | 23 50 (46%) |
| Overall Rates (a) | | | |
| Adjusted Rates (h) | 24.3% | 45.1% | 49.8% |
| Terminal Rates (c) | 7 38 (18%) | 12 33 (36%) | 16 39 (41%) |
| Life Table Tests (d) | P=0.013 | P=0.042 | P=0.014 |
| Incidental Tumor Tests (d) | P=0.009 | P=0.098 | P=0.019 |
| Cochran-Armitage Trend Test (d) | P=0.004 | | |
| Fisher Exact Tests | | P=0.052 | P=0.005 |
| Forestomach: Squamous Cell Papilloma | | | |
| Overall Rates (a) | 3 49 (6%) | 3 48 (6%) | 9 49 (18%) |
| Adjusted Rates (b) | 7.9% | 9.1% | 23.1% |
| Terminal Rates (c) | 3 38 (8%) | 3 33 (9%) | 9 39 (23%) |
| Life Table Tests (d) | P=0.038 | P=0.597 | P=0.065 |
| Incidental Tumor Tests (d) | P=0.038 | P=0.597 | P=0.065 |
| | | | |
| Cochran-Armitage Trend Test (d) | P=0.034 | | |

788K

Benzyl Acetate

HIGH DOSE

| | | | === | === | | | | | | | | | | | | | | | | | | | === | | | |
|--|--|-------------|----------|----------|----------|----------|----------|----------|----------|----------|----------|----------|----------|--------------|----------------|------------|--|--|----------|----------|----------|-----------------|----------|----------|----------|-------------------|
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| RESPIRATORY SYSTEM | 1-51 | -21 | اد | -31 | 51 | -21 | - 31 | 31 | . د | -81 | .51 | | -51 | _51_ | 51 | 51 | 21. | ٤١. | ئق | -51 | _51 | _51_ | -51 | _51 | -51 | |
| LUNGS AND BRONCHI HEPATOCELLULAR CARCINOMA, METAS ALVEOLAR/BRONCHIOLAR ADENOMA ALVEOLAR/BRONCHIOLAR CARCINOMA | + | ٠ | • | + | + | • | + | + | • _x_ | ٠ | • | • | + | + x | + × | + | • | + X | ž | • | ٠ | • | + | ٠ | ٠ | 50 1 6 2 |
| TRACHEA | | + | + | + | + | • | + | + | + | + | + | + | + | + | + | + | + | + | - | + | + | + | + | + | + | 49 |
| HEHATOPOIETIC SYSTEM | | | | _ | _ | | | | _ | | _ | | _ | | | | _ | - | - | | | | _ | | ┥ | |
| DONE MARRON | 1 | * | + | +_ | + | + | ٠ | + | + | ٠. | + | | + | + | + | <u>.</u> | <u>.</u> | ٠. | + | + | + | + | + | , | ٠ | |
| SPLEEN Hemangiosarcoma | <u> </u> | • | + | <u>.</u> | • | + | + | + | + | <u>.</u> | + | + | + | + | + | + | + | + | - | + | <u>.</u> | + | + | + | + | 49 |
| LYMPH HODES MALIGHANT LYMPHOMA, MIXED TYPE | <u> :</u> | + | + | + | <u>+</u> | + | + | + | + | + | <u>+</u> | • | • | • | + | ٠ | + | + | + | ٠ | <u>.</u> | + | + | + | ٠ | 51 |
| THYMUS | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | - | + | + | + | + | + | + | 49 |
| CINCULATORY SYSTEM | | _ | | _ | _ | | | _ | | _ | _ | _ | | | - | | | | | - | _ | | _ | | -{ | |
| HEART | + | + | + | + | + | + | + | + | + | ٠ | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| DIGESTIVE SYSTEM | _ | _ | | _ | | | _ | | _ | _ | | _ | | | | | - | _ | _ | _ | _ | _ | | _ | + | |
| SALIVARY GLAND | + | ٠ | + | + | ٠. | • | <u>.</u> | ٠. | + | <u>+</u> | * | ٠. | + | <u> </u> | + | ٠_ | <u>.</u> | <u>.</u> | + | * | * | <u>+</u> | <u>+</u> | • | + | 49 |
| LIVER | + | + | + | + | + | + | + | + | + | + | ٠ | + | + | + | + | + | + | + | + | + | + | + | + | ٠ | + | 58 |
| NEOPLASM, HOS HEPATOCELLULAR ADENOKA HEPATOCELLULAR CARCINOMA | ٠ | x | | x | | | x | | × | x | x | | | | x | <u>x</u> _ | x | x | <u>x</u> | x | | | × | | × | 13 13 |
| BILE DUCT | | + | <u>+</u> | + | * | + | + | + | + | ٠. | + | <u>.</u> | + | + | <u>+</u> | <u>.</u> | + | + | + | + | + | <u>+</u> | + | + | + | |
| GALLBLADDER & COMMON BILE DUCT | <u> </u> | + | + | + | + | .+ | <u>+</u> | N_ | + | + | + | + | <u>+</u> | +_ | • | <u>+</u> | <u>.</u> | ٠. | H | + | + | + | ٠. | +_ | -+ | 5 £ ¥ |
| PANCREAS | <u> </u> | <u>+</u> | • | + | + | + | <u>+</u> | + | + | <u>+</u> | • | + | +_ | + | + | <u>+</u> | <u>+</u> | + | | ÷ | * | <u>+</u> | ٠. | ± | ٠ | 49 |
| ESOPHAGUS | 1 | <u>+</u> | ٠ | + | + | <u>+</u> | ٠. | <u>.</u> | + | + | ٠ | ٠ | + | + | + | + | <u>+</u> | + | - | +_ | | <u>*</u> | • | | ٠ | - 63 |
| STOMACH SQUAMOUS CELL PAPILLOMA SQUAMOUS CELL CARCIMONA | • | • | ٠ | + | * | + | + | + | + x_ | • | + | • | * | + | * | * | + | + | - | + | + | * | + | + | + | 49 9 2 |
| SMALL INTESTINE | | * | • | + | + | + | • | - | + | + | • | • | • | + | + | + | ŧ | • | - | + | + | + | · | • | + | 47 |
| LARGE INTESTINE | + | • | + | + | + | + | • | + | + | | | + | + | • | + | + | • | + | - | + | + | + | + | + | + | 46 |
| URINARY SYSTEM | +- | | | | _ | | _ | _ | _ | | | | | | | | _ | _ | _ | | | | - | | \dashv | |
| KIDHEY TUBULAR-CELL ADENONA TUBULAR-CELL ADENOCARCIHOMA | + | * X | + | + | + | + | + | + | + | • | • | ٠ | + | + | * | + | + | + | + | + | + | + | + | • | + | 58 |
| URIHARY BLADDER | + | + | + | + | + | + | + | + | + | + | + | + | + | + | - - | + | + | • | - | + | + | + | + | Ţ | + | 49 |
| ENDOCRINE SYSTEM | ├ | _ | _ | —- | _ | | | | | | | | | | | | - | _ | _ | _ | _ | | | | -+ | |
| PITUITARY | 1 | + | | + | ٠ | + | ٠ | + | + | + | + | + | + | <u>.</u> | + | | ٠ | <u>. </u> | - | + | + | + | + ' | | + | - 66 |
| ADRENAL GANGLIOHEUROMA | 4 | + | + | ţ. | + | + | + | + | ٠ | <u>+</u> | + | + | + | ٠ | + | + | • | • | + | <u>+</u> | • | ٠ | + | + | ٠ | 49 |
| THYROID | + | ŧ | + | ÷ | + | + | + | + | + | + | + | + | + | + | + | + | + | + | - | + | + | + | + | - | - | 47 |
| FOLLICULAR-CELL ADENOHA PARATHYROID | - | ٠. | _ | <u>م</u> | _ | _ | _ | | _ | _ | _ | _ | _ | | _ | | . - | | _ | | | | _ | | 1 | |
| PANCREATIC ISLETS ISLET-CELL ADENOMA | <u> </u> | + | + | • | + | • | ÷ | + | + | <u>*</u> | + | + | + | - | - - | • • | <u>. </u> | <u>.</u> | - | + | <u>-</u> | + | <u>*</u> | + | 7 | 47 |
| REPRODUCTIVE SYSTEM | _ | | | | | | | | | _ | _ | | | | | | | | | | | | × | | _ | z |
| MAMMARY GLAND | , | u | u | u | ע | N | | н_ | . N | ж_ | н_ | | | N_ | H | N | М. | × | H | н | N | H | u | v | | |
| TESTIS INTERSTITIAL-CELL TUMOR | + | | + | + | + | + | + | + | + | + | + | + | + | | _ | | | | + | + | + | | + + | + | + | 51 ₂ |
| PROSTATE HERVOUS SYSTEM | 1 | + | ٠ | | <u>+</u> | <u>-</u> | ÷ | + | ÷ | + | • | _ | <u>.</u> | + | ÷ | - | _ | +_ | - | ÷ | ÷ | <u>-</u> | +_ | ÷ | 4 | 69 |
| BRAIN | ١. | + | + | | | + | ÷ | | + | + | + | + | + | | + | + | | | + | + | + | + | | | + | 50 |
| SPECIAL SENSE ORGANS | <u> </u> | _ | _ | | _ | | _ | <u>.</u> | <u> </u> | | | _ | _ | _ | _ | | _ | _ | _ | <u> </u> | | | _ | <u>.</u> | 4 | |
| HARDERIAN GLAND ADENOMA, NOS | н | ĸ | ĸ | H | N | Ħ | H | ĸ | H | н | H | H | H | H | н | ĸ | ĸ | H | H | H | н | H | H | ĸ | H | 50± |
| DODY CAVITIES | - | _ | _ | | | | _ | | _ | | | | _ | | | _ | | | | | | — | | | + | |
| MESENTERY HEPATOCELLULAR CARCINOMA, METAS | H | H | H | H | H | H | H | н | H | ĸ | H | H | ĸ | H | ĸ | ĸ | н | н | ĸ | н | н | H | H | H | H | 50= 1 |
| ALL OTHER SYSTEMS | - | _ | | | _ | | | _ | | | | | _ | | _ | | | _ | _ | | | | _ | _ | + | |
| MULTIPLE ORGANS NOS HEPATOCELLULAR CARCINOMA, METAS HALIGHANT LYMPHOMA, NOS HALIGLYMPHOMA, LYMPHOCYTIC TYP | н | H | H | H | H | N Y | Ħ | × | ĸ | Ħ | H | ĸ | ĸ | N | H | н : | H | × | H | N | H | H | H | H | N | 50x |

ANIMALS NECROPSIED

Renaul Acetate

This is for 25 of the 50 mice in the high dose group of males

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DAMINOZIDE (alan)

| Male Rats | | | |
|---|--------------|---------------|----------------|
| | Control | Low | High |
| Lung: alveolar/bronchiolar adenoma or carcinoma Pituitary: chromophobe adenoma Adrenal: pheochromocytoma or pheochromocytoma, | 1/20 0/18 | 3/50 2/43 | 0/50 2/49 |
| malignant | 2/20 | 2/50 | 2/50 |
| Thyroid: C-cell carcinoma | 0/16 | 0/38 | 2/43 |
| Thyroid: C-cell adenoma or carcinoma | 2/16 2/20 | 3/38 1/50 | 2/43 4/50 |
| Preputial gland: adenoma or carcinoma, NOS Testis: interstitial-cell tumor | 13/20 | 46/50 | 4/50 47/50 |
| Female Rats | | | |
| Lung: alveclar/bronchiolar adenoma | 0/20 | 0/50 | 4/48 |
| Hematopoietic System: leukemia | 0/20 | 4/50 | 1/50 |
| Pituitary: chromophobe adenoma Pituitary: chromophobe adenoma or carcinoma | 0/19 3/19 | 3/45 10/45 | 0/43 8/43 |
| Thyroid: C-cell carcinoma | 2/15 | 1/38 | 0/44 |
| Thyroid: C-cell adenoma or carcinoma | 4/15 | 3/38 | 2/44 |
| Mammary Gland: fibroadenoma | 3/20 | 9/50 | 2/50 |
| Uterus: leiomyosarcoma | 0/19 | 1/50 | 3/50 |
| Uterus: endometrial stromal polyp | 0/19 | 6/50 5/50 | 4/50 |
| Uterus/Enclometrium: adenocarcinoma, NOS Mesentery: lipoma | 0/19 0/20 | 5/50 0/50 | 3/50 2/50 |
| Weserkery apoint | 0,20 | 0/00 | 200 |
| Male mice | | - /m- | |
| Lung: alveolar/bronchiolar carcinoma | 2/14 | 9/50 | 12/46 |
| Lung: alveolar/bronchiolar adenoma or carcinoma Hematopoietic System: lymphoma or leukemia | 4/14 2/14 | 15/50 6/50 | 18/46 11/46 |
| Liver: hepatocellular carcinoma | 0/14 | 7/50 | 13/46 |
| Liver: hepatcoellular adenoma or carcinoma | 1/14 | 9/50 | 14/46 |
| Female mice | | | |
| Lung: alveolar/bronchiolar carcinoma | 1/20 | 4/39 | 2/48 |
| Lung: alveolar/bronchiolar adenoma or carcinoma | 1/20 | 8/39 | 10/48 |
| Hematopoietic system: all neoplasms | 5/20 | 16/41 | 14/48 |
| Hematopoietic system: malignant lymphoma, lymphocytic | | | . = = |
| leukemia, or leukemia, NOS | 5/20 | 14/41 | 13/48 |
| All sites: hemangioma Liver: hepatocellular carcinoma | 0/20 0/20 | 4/41 3/40 | 0/48 0/48 |
| Liver: hepatocellular adenoma or carcinoma | 1/20 | 4/40 | 0/48 |
| Pituitary: chromophobe adenoma | 2/14 | 1/19 | 0/14 |
| Uterus: endornetrial stromal polyp | 0/20 | 3/37 | 0/45 |
| Peritoneum: lipoma | 2/20 | 0/41 | 0/48 |
| Mesentery: lipoma | 2/20 | 1/41 | 0/48 - |

Risk Analysis in Environmental and Occupational Health September 1, 1987

Uncertainties in Predicting Human Risks

Edmund Crouch

1. Background Information

It is useful to bear in mind a few sobering facts about total populations at risk, and the normal total risk of death and of dying of cancer. For the U.S., the total population is about 240 million, while the annual number of deaths is about 2 million per year and the annual number of cancer deaths is about 400 thousand. These figures imply an annual average total risk of death of about 10^{-2} (1 percent per year), and a lifetime risk of cancer of about 0.2 (20 percent, or 200,000 x 10^{-6}), estimates you can obtain simply by dividing one figure by another.

Of course, simply dividing one by another is not a particularly accurate way of computing such estimates -- one should do the correct thing and take the age structure of the population into account, and the variation of risks with age, and so on. But even when you do precisely that, the average lifetime risk of cancer comes out to be about 20 to 25 percent. We can expect this figure to get higher as the expectation of life increases, and as other causes of death are eliminated (assuming -- pessimistically -- that most cancers cannot be eliminated). It is mainly the increase in expectation of life which has made cancer such a prominent cause of death in the (historically) recent past, because cancers tend to be diseases of old age.

For many cancers it is found that the death rate varies as a power of age:-

rate ~ ageⁿ

where the exponent n is in the range 4 to 11. For such cancers, this pattern seems to hold over the age range from about 30 to 65. At lower ages the rates tend to be very small but almost independent of age (and the cancers may be completely different diseases in youngsters), while at higher ages the reported death rates are lower than would be predicted by this sort of formula - and in some cases the reported death rates are actually lower for old enough groups. It is unclear whether these reductions in death rates in the elderly are real, or are simply due to a difference in the accuracy of diagnosis and reporting. It is also possible that the reduction in reported death rates is real, but is due to the winnowing out of the population of those who are susceptible to these particular cancers, leaving a core of more resistant individuals.

The major exceptions to the power law variation of death rate with age are the cancers which are known to be hormonally dependent (e.g. breast cancer), or are highly curable (skin cancers), or in which the natural progression is altered by intervention (e.g. a high proportion of women have had hysterectomies by age 65, so that they cannot be at

risk of uterine cancers thereafter).

With this age variation of risk of cancer understood, we can now oversimplify again and quote a lifetime average annual risk for cancer, obtained simply by dividing the lifetime risk by an average lifetime of about 70 years. This give an average annual risk of about $2 - 3 \times 10^{-3}$. Notice that we are here averaging over a lifetime -- the figure is not meant to imply that the risk is the same in each year of life -- we have just seen that it varies drastically with age.

When discussing the risks of carcinogens, the same caveats have to be borne in mind. We usually attempt to estimate a lifetime risk, but may express this, for comparison purposes, as an annual average risk. For an individual exposed continuously to a carcinogen, we would expect that the risk of cancer increases with age in a fashion similar to the risk of other (naturally occurring) cancers.

There is another reason also for quoting an annual average risk obtained by averaging over a lifetime. When estimating risks of carcinogens, one is often interested in the response of a population to exposure to the carcinogen. In this case, one should strictly (if it were possible) estimate what the effects at all future times would be on individuals of different ages at the times of exposure. The effects at all future times on the whole population would then be an average over the effects on all the individuals in the population (who were of different ages at the times of exposure.

Thus, to obtain an estimate of the effects on a population, one implicitly performs an average over the age groups present in the population. If the population were stationary (and if certain other conditions were fulfilled) this average would be the same as an average over a lifetime. This explains the usefulness of a lifetime average, since one may argue that the differences between population and lifetime averages are small compared with other uncertainties inherent in all the procedures we will describe later.

The preceding discussion must be considered only a heuristic argument for accepting a lifetime average as being useful. In practice, people will be exposed at different ages, and for varying periods, to different amounts of carcinogens. All these differences (and many more besides) will affect the probability of carcinogenesis for each of them.

2. Known Human Carcinogens

There is now good evidence that human exposure to certain materials can, under certain conditions, increase the rate of human cancer. The evidence comes from various types of epidemiological investigation (discussed in other talks in this course). In all cases, exposures to these materials has been high, compared with population exposures, and the population exposed has been small compared with the total U.S. population. The resultant risks to those exposed has been substantial.

The following table indicates a few of these materials, and the types of cancer which have been caused in humans by exposure to them.

Also shown are the "natural" rates for such cancers, expressed in terms of lifetime risk and annual average risk.

| Material/Action | Site or Type | Lifetime Risk (In absence | ce of expo | Annual Average Risk sures) |
|--|--------------------|---|------------|-------------------------------------|
| 4-Aminobiphenyl Auramine manufacture Benzidine Chlornaphazine Cyclophosphamide 2-Naphthylamine | Bladder | 5 x 10 ⁻³ | | 7 x 10 ⁻⁵ |
| Arsenic (compounds) Asbestos BCME CCME Chromium (VI compounds) Mustard gas Nickel refining | Lung | 4 x 10 ⁻² (Pop ⁿ . ave. | .) | 6 x 10 ⁻⁴ |
| Arsenic PUVA Socts, Tars, Mineral oils | Skin | 3, x 10 ⁻³ | (Deaths!) | 4 x 10 ⁻⁵ |
| Vinyl chloride | Liver | 1 x 10 ⁻³ | | 2×10^{-5} |
| DES (In Utero) | Vagina | 7×10^{-3} | | 9×10^{-5} |
| Benzene Myleran Chlorambucil Melphalan | Leukemia | 8 x 10 ⁻³ | | 1 x 10 ⁻⁴ |

Typically, in epidemiological studies, a relative risk of >2 is required in order to detect any effect. Thus the (epidemiologically) discoverable population average human risks are $>10^{-5}$ per year, or 10^{-3} per lifetime, and probably much larger. For the small subgroups of the population usually available for study, the observable risks are generally much larger.

3. Target Risks. The Necessity of Extrapolation.

When considering the size of acceptable risks to the public at large, the usual targets are much smaller than the discoverable risks discussed above. Typically they will be of order $< 10^{-6}$ per year. Note that the EPA and the FDA set targets of order 10^{-6} per lifetime, that is, of order 10^{-8} per year.

It must also be borne in mind that there are a large number of materials which are of potential interest. The Chemical Abstracts

Service (CAS) has now given names to well over six million distinct chemicals which have been mentioned in scientific literature, and there have been various estimates of the number (around 50,000) of chemicals in general commercial use.

With such numbers, it should be immediately apparent that there are just too many time, money and logistical constraints to directly detecting any adverse effects from such a plethora of materials to which humans may be exposed. Notice that a risk of 10^{-6} per lifetime corresponds to a rate of about 3 per year in the whole U.S. population. Thus, even if the whole U.S. population were exposed to some material causing a risk of death of 10^{-6} per lifetime, the resulting deaths would be statistically indistinguishable in the usual two million deaths per year (unless there were something extremely unusual about the deaths).

Extrapolation is therefore essential in order to estimate the sizes of risks, and hence be in a position to demand that risks be reduced to the levels mentioned. The fundamental observation on which such extrapolation is based is that:

HUMAN CARCINOGEN -->implies--> ANIMAL CARCINOGEN

In other words, every known material which has been shown to be a human carcinogen is also known to cause tumors in animals under suitable conditions. The only current possible exception to this is arsenic, but it is quite plausible that this is simply because it has not been tested adequately.

This observation is not very useful in itself, but what is done in order to allow risk assessments is to assume its converse:

ANIMAL CARCINOGEN -->implies--> HUMAN CARCINOGEN

and to work from here. This assumption is not unreasonable, in view of what is known about carcinogenesis - although it is something which can be argued about in specific cases.

4. The Nature of Carcinogenesis.

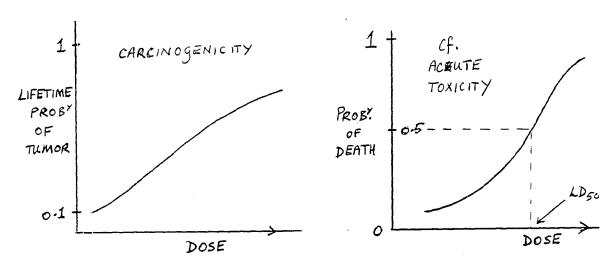
In what follows, it is useful to keep in mind some information about the process of carcinogenesis. This information has been derived from studies of humans and animals, and from experiments performed in vivo or in vitro. It is based partly on experimental studies, and partly on theoretical ideas suggested by those studies.

- (a.) Cancers arise from one (or more) individual cell(s) which have gone "out of control" in some way the cell becomes immortal, with no limit on the number of cell divisions, and the usual constraints on cell division no longer apply. A cell may pass through several stages before reaching this state.
- (b.) The underlying cause of such behavior is probably some effect(s) on the genetic material of the cell, but the exact mechanism(s) is (are) unknown.

- (c.) The occurrence of such events appears to be a random process at some level. One cannot tell which individual cell or animal or person will be affected. Hence we talk about the PROBABILITIES of cancer the chance that some event will occur.
- (d.) When we feed materials to experimental animals, these probabilities depend on various factors which can be manipulated. For example, they vary with:

The total AMOUNT of material (the total dose)
The AGE at which dosing takes place
The RATE OF APPLICATION, or the time over which dosing continues
OTHER FACTORS (some known -- stress, dietary factors, ...,
others unknown)

We therefore expect, and in practice observe, DOSE-RESPONSE curves. Such dose-response curves are fundamental in extrapolating risks to humans. I like to draw an analogy to the similar problem of extrapolation which arises for acute toxicity -- in both cases, we have measurement difficulties at low doses, and in both cases there is some sort of dose-response relationship (which I deliberately leave vague for now):



- (e.) Evidently there will be some AGE STRUCTURE to the probabilities of cancer. As mentioned, for many cancers in humans the death rate from cancers increases with a power of age. In experimental studies involving long term feeding of rodents, the same sort of age structure is found for the incidence of tumors. A "LIFETIME" probability thus depends on how you measure it the usual practice is to assume a "standard" lifetime of ~70 years for humans and ~2 years for rodents.
- (f.) At high enough doses (i.e.. at high RESPONSES one sees interactions between different materials in both animal experiments and in human data (e.g. smoking and alcohol consumption, smoking and radon exposure, smoking and asbestos exposure). The effect of such interactions is to make the effect of two or more materials different from the sum of the effects of the materials individually (at the same

doses).

- (g.) It is not possible to make direct measurements of what happens at low doses (i.e. at LOW RESPONSES). In this context, low dose means a dose at which the response probability is < 0.1 usually, and < 0.01 certainly. Any attempt at studying lower doses runs up against problems of logistics, cost and the background cancer rate.
- (h.) The shape of dose-response curves assumed for the low dose regions are thus based on:

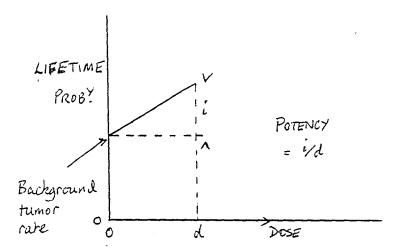
Theoretical ideas

Prejudice

Guesswork

For performing risk assessments for human safety purposes, there is naturally a prejudice to be conservative.

It is generally agreed that assuming LINEARITY between dose and response (for our discussion, this means the lifetime probability of a cancer) at low enough doses is CONSERVATIVE. This assumption is made in a theoretical way -- it is assumed that the true relationship between dose and response lies, at low enough doses, entirely below (or at worst on) a linear curve joining the response at zero dose (background) with the response at some higher (but still low) dose.



Typically, the background rate is of order 10^{-4} to 10^{-1} , and we are interested in excesses over the background of order 10^{-6} to 10^{-4} , so this diagram is not to scale. It is useful to define the POTENCY of a carcinogen as the ratio of excess lifetime probability of cancer to the dose causing that excess (at low enough doses). On the diagram, this is the ratio i/d. The potency is thus the slope of the dose-response curve at low enough dose, and we have the basic equation:

EXCESS RISK = POTENCY x DOSE

There is reasonable evidence that some mechanisms of carcinogenesis result in a THRESHOLD -- i.e. that there is some (threshold) dose below which the excess incidence of cancer is much lower than would be

predicted by a linear extrapolation from doses above the threshold, and possibly that the excess incidence of cancer is literally zero below such a threshold (excess, here, means excess over the background occurrence of cancer). Some of the evidence for such mechanisms comes from observation of the dose-response curves in experimental situations -- the experiments on saccharin provide a good example. However, there is still the possibility that a linear mechanism may still operate at low enough doses, and so any human risk assessment has to take that possibility into account.

5. The Standard Animal Test.

The requirements for a "standard" animal test are quite severe. The animals involved have to be as similar to humans as possible -- in metabolism, in being omnivorous, in their sensitivity to chemicals, for example -- yet as different as possible in their life span and cost of upkeep (so that we can get results in a reasonable time at a reasonable cost). In practice, there is little option but to use standard laboratory animals. The usual choices are rodents -- rats and mice; with occasional tests being performed on golden hamsters or guinea pigs. Other animals (e.g. gerbils) have been proposed, but for now the experience built up in handling laboratory rodents is a strong incentive for continuing their use despite certain known disadvantages. Any change would now have to be done gradually, and with much cross checking with previous results.

It is now standard to require tests to be performed in at least two species (practically always rats and mice) and on both sexes, in case one or the other species or sex is peculiarly resistant to the material under test. A compromise has to be made over the number of animals to test. It would be desirable to have as many as logistically possible, to increase the statistical sensitivity of the experiment; but as few as possible to minimize the costs of testing (since there is always another material to test). The current recommendation is for at least 50 per group of similarly treated animals.

There is a similar trade-off between costs and the number of dose levels to test in a given experiment. The current recommendation is to have at least three dose groups -- an undosed group (the control group), a group tested at the maximum tolerated dose (MTD) of the material under test, and the third group tested at some intermediate dose (usually 1/4 to 1/2 of the MTD).

The MTD of a material is roughly defined to be as much as possible, but not enough to kill off the animals early or to cause too large other overt effects (like loss of weight). The reason for using it in these experiments is to increase the sensitivity, on the basis that giving more of something is more likely to produce a response if any response if going to happen at all. The sensitivity has to be as high as possible, since the observable responses are of the order 10^{-1} (10%) while the risks of interest are of order 10^{-6} (100,000 times smaller). The alternative way of increasing sensitivity is to increase the number of animals tested (within reason), but this only increases sensitivity in proportion to the square root of the numbers tested, while increasing

the dose gives an increase in sensitivity roughly proportional to the dose. Clearly the latter is most cost effective.

Even with such a minimum design, there are:

3 dose groups x 2 sexes x 2 species x 50 animals per group

giving a minimum of 600 animals per experiment. All the animals have to be carefully housed (under standard conditions), cared for, and individually tracked throughout their two year lifetime. They are then sacrificed and a large number of their tissues examined individually. None of this comes cheap -- the cost of such an experiment is unlikely to be less than \$200,000, and may run above \$1,000,000.

It should be noted that the type of experiment detailed here is the minimum considered necessary to answer a YES/NO question: Is this material carcinogenic under the conditions of this standard bioassay? The experimental design and analyses performed are designed to be unlikely to answer YES if there is no carcinogenic action present (so that the experiments have low alpha error), but they can easily answer NO even in the presence of carcinogenic action. This sort of test is exactly what is required, of course, if one is interested in identifying materials which are surely carcinogens; in order to study their mechanism of action for example -- one doesn't want to accidentally end up with a material with no carcinogenic action.

I would submit, however, that for the purposes of protection of public health, the questions asked of the tests are entirely the wrong way round. For protecting public health, one should surely ask not whether this material is almost surely a carcinogen, but how strong a carcinogen it could be, given the results of the experiment. The fact that the same sort of analysis is applied now as in the past is perhaps a combination of accident and inertia, but one has to admit that, for the most part, the methodology has been largely successful so far.

6. Raw Results - and what to do with them.

Having spent 2 years performing the experiment described above, what output do we get? When the animals are sacrificed, they are dissected and a whole list of tissues examined, both macroscopically and microscopically. All lesions, whether related to cancer or not, are noted down and usually (nowadays) recorded in some sort of computer database. The pathologists performing the examinations usually use some sort of standardized nomenclature for what they observe -- for example, the National Toxicology Program uses a modified version of the Systematized Nomenclature for Pathology (SNOP). Other information about individual animals is also recorded -- such information as where they came from, which cages they were kept in, when they died (e.g. if they died naturally, or were sacrificed at the end of the experiment, or sacrificed earlier because they clearly would not survive), and so forth.

The outcome is that for each animal, we have a list of the lesions affecting them when they died. An example of a condensed listing of just

the cancer-related lesions is appended. From such listings, we can perform various analyses and statistical tests to see whether the rate of cancer was increased at any site or for any type of cancer.

The simplest sort of analysis can be performed if all the animals survived for the whole length of the experiment -- and in practice the same sort of analysis is performed provided a reasonable fraction survived that long and provided there were not too many early deaths. In that case, we can simply list the dose groups and the numbers of animals with tumors compared with the total number of animals examined;

| Dose | Number with Tumor | Numbe Exami | - | |
|------------------------|-------------------------|----------------|-----|---------|
| 0 (control) 0.5 MTD | 10 25 | 50 50 | for | example |
| MTD | 30 | 50 | | _ |

However, things are not this simple. Similar results are available for

- o Many different sites (See below
- o Many different tumor types (for examples)
- o Combinations of these

To determine whether the rate of cancer has been increased involves comparing the proportion with tumor in the control group with the proportion with tumor in the dosed groups, and deciding whether there is a significant increase in any dosed group(s). The choice of which sites and/or types of tumors to combine before performing such statistical tests can be difficult. Generally, various grades of tumors (nodules, adenomas, carcinomas) may be combined for any given site. Table 2 gives an example of the sort of combination and testing which is performed.

In addition to the simple numbers of animals with tumor, there is additional information available which may be used in more complicated cases. The date of death of each animal is recorded, and may be taken into account in time-adjusted analyses of tumor incidence and in the life-table tests mentioned on the appended material.

For risk assessment purposes, it is necessary to make various assumptions about the behavior of animals in experiments like these. For example, it is assumed that:

- o Animals are affected independently (a tumor in one animal has no effect on any other animal).
- o Animals are equally likely to be affected
- o Each animal receives the same dose

.

It is assumed that cage effects, littermate effects, the effects of heating, lighting, stress etc. are either not present, or are randomized among all the animals in such a way that there will be no effect on the final analysis.

With such assumptions, the probability of an animal having a tumor is related to the dose by some sort of dose-response relationship, so that at any given dose this probability can be computed. The observed results, a number of animals with tumor out of a larger number examined,

is then a binomial sample with this probability. In practice, we don't know what the dose-response relationship is - we wish to estimate it from the results. But we assume that we know the SHAPE of the dose-response relationship (specified by a mathematical formula), so that all that is required is to estimate some PARAMETERS in the mathematical formula.

For example, the E.P.A. uses a dose-response relationship of the form:

$$p = 1 - \exp\{-(q_0 + q_1.d + q_2.d^2 + ... + q_{k-1}.d^{k-1})\}$$

when there are k doses in an experiment, where p is the lifetime probability of tumor at dose d. It is usual to use a maximum likelihood technique to estimate the various parameters $q_0, q_1, q_2, \ldots q_{k-1}$, given the observed numbers of animals with tumors and the numbers of animals examined at each dose.

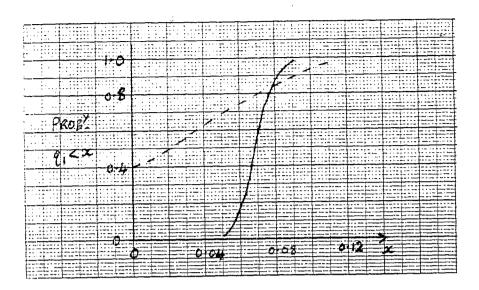
In cases where there is appreciable early mortality in the experiment, so that the observed numbers of animals with tumors are likely to be underestimates of what would have been observed at the end of a perfect experiment, one can make modifications to the dose response relationship, just as one can make life-table adjustments to standard statistical tests. One technique used is to modify the dose response curve to explicitly include length of life, using the idea that probability of tumor is likely to increase with a power of age (see page 1):

$$p = 1 - \exp\{-(q_0 + q_1.d + q_2.d^2 + + q_{k-1}.d^{k-1}) \ (t/L)^n\}$$

where t is the age at death, and L is a standard lifetime. The parameter n can either be fixed at some reasonable value (in the range 2 to 11), or estimated from the experimental results. This technique suffers from the same limitations as the usual modifications to the standard statistical tests -- one has to introduce additional assumptions in order to apply it. In this case, one has to decide whether the tumors were a cause of death, or simply incidental.

An alternative technique used when there is early mortality is to estimate the age dependence directly from the data, using a (so-called) non-parametric technique. This approach has been used to assemble a large database of comparable analyses of animal bioassays.

This methodology has taken the raw results of the animal experiment, and summarized them in the form of a dose-response curve with known parameters. It is also possible to estimate how uncertain one is about a given parameter, using the same maximum likelihood techniques used to obtain point estimates of them - indeed, one can plot the uncertainty distribution for any of the parameters. For example, for the parameter q_1 (which will turn out to be the one of interest), we can plot the probability that q_1 lies below any given value:

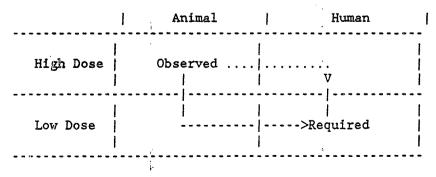


In particular, we can find that value q_1^* such that there is 95% probability that $q_1 < q_1^*$.

However, it is important to note that the uncertainty distribution so plotted contains only the uncertainty due to the numerical size of the experiment -- the uncertainty that arises because we used a small number of animals, instead of an infinite number. It does not include the uncertainties which must be present because of the shakiness of all our assumptions.

7. The Two Major Extrapolations

The assumptions made so far have allowed us to parametrize an animal dose-response relationship, obtaining values for the parameters which are presumably reasonably appropriate for high doses. Strictly speaking, this parametrization of the dose-response curve only enables us to estimate the results we would expect to see at high doses in animals - the dose-response relationship can only be relied on to interpolate between high doses and perhaps to extrapolate a short distance outside the experimental range of doses. The problem now is to perform two extrapolations - from animals to humans, and from high dose to low dose:



LOGICALLY there are two distinct routes to follow in this extrapolation, since there are logically two distinct dose-response

curves involved (see below). One can extrapolate from high dose to low dose using the ANIMAL dose-response curve, and then extrapolate to humans (dashed lines), or extrapolate to humans at high doses and then use a HUMAN dose-response curve to extrapolate to low doses.

We have seen how to estimate the parameters of the (high dose region of) the animal dose-response curve. In practice, the same curve (with the same parameters) is is used to extrapolate to low doses, by building into the mathematical structure of the dose-response curve all our assumptions about low dose behavior.

How is this relevant for estimating human risk? Consider a generalized situation in which we wish to estimate the response (R) of humans to some dose (D) of material, when there is a response (r) in some animal at dose (d). Notice that nothing implies that r, R measure the same sort of response - they could be completely different (r could be acute toxicity to the lung of a mouse, R could be skin rashes in humans). Similarly, the dose measures d, D may be completely different. In the case immediately at hand, r is the lifetime probability of tumor in animals, and d is a dose as measured in the animal experiment. There are other cases of practical importance however - r might be some measure of response (such as number of revertants per culture dish) in a mutagenesis bioassay, with d the dose applied to each culture dish.

Human

Response: r R (lifetime probability of tumor, p) Dose measure: d D (as used in experiments) Dose-response curve: r = f(d; a,b,c,...t) R = F(D; A,B,C,...T) [p = 1 - exp{-(q0+q1.d +...)}]

Animal

What is required is some connection between the parameters a,b,c,... of the animal dose-response relationship and the parameters A,B,C,... of the human dose-response relationship. These parameters presumably include those mentioned in section 6, and I have explicitly included age amongst them. Given such a connection, the extrapolation to humans of the results in the animal studies is perfectly straightforward. The problem lies in finding the connection.

Once such a connection is found (by whatever means) we have the methodology for the two extrapolations required. Notice the difference between what is done in the two distinct pathways of extrapolation mentioned above:

In the first, the shape of the dose-response curves are examined, and it is decided how they may be (separately) extrapolated to low doses. Then some relationship is postulated between the parameters of the dose-response curves at low doses (it has to be postulated, since nothing can be measured at such low doses). One potential advantage of this approach is that the animal dose-response curve could be measured, in principle and by heroic experimentation, down to lower response rates than usual (and this has been done in some cases) - allowing greater confidence in this extrapolation to low dose.

In the second, some relation between the parameters of the dose-response curves is obtained at high doses (and this may be done experimentally, in principle, since at high doses the responses are measurable). Then it is decided how the human dose-response curve should be extrapolated to low doses. The advantage here is the possibility of direct comparison between species, albeit at high dose.

The difference between these two logically distinct routes of extrapolation might be important in some circumstances. For cancer risk assessment based on animal carcinogenesis bioassays, however, the distinction is glossed over (one might even say, ignored), by the practice of assuming the same mathematical form for the dose-response curve in both humans and animals (or more generally, in all species), and interpreting the parameters in the same way for both compared species.

In the general case, however, what is required is some sort of relationship between the parameters of the dose-response curves:

Animal Human
$$r = f(d; a,b,c...t)$$
 $R = F(D; A,B,C...T)$

We need to be able to derive the parameters A,B,C... from the values a,b,c which can be estimated from experiments, and then use the human dose-response curve to extrapolate to low doses.

The practical approach is to seek parametrizations of the dose-response curve which result in the derivation of A,B,C... being simple given a,b,c... Consider the case of acute toxicity, for example. It is found that the shape of the dose-response curve for acute toxicity, in which the response is death, is very similar for a large number of toxins and for many different species. There is, in this case, a threshold-type dose-response curve which can be nicely parametrized by two values: the dose at which 50% of the animals tested can be expected to die (under suitable conditions), and the slope of the dose-response curve at this dose. The first parameter is known as the LD50 (the second has no special name).

Why is this parametrization useful? If the $\rm LD_{50}s$ of various materials in one species are plotted against the $\rm LD_{50}s$ of the same materials in another species, one finds approximate proportionality between them (the plot is a straight line). This can be expressed as, for example,

 LD_{50} (rabbit) is proportial to LD_{50} (mouse).

Even more remarkable, it turns out that if the dose is measured in a suitable way, as (amount)/(surface area of animal), then approximately we actually have

 $LD_{50}(rabbit) = LD_{50}(mouse) = LD_{50}(other species)$

and it is this approximate equality which explains the utility of the ${\rm LD}_{50}$. The other parameter used in defining the dose-response curve, the slope of the curve at the ${\rm LD}_{50}$, is not involved in this relationship.

Had we chosen some other method of parametrization, it is quite possible the required interspecies relationship between parameters would be much more complicated.

8. Interspecies Comparison - Constant Relative Potency

What is sought is a simple relationship between the parameters of dose-response relationships in different species. When it is assumed that the dose-response relationship includes a term linear in dose, there is a simple measure of the strength of a carcinogen - the carcinogenic potency (the slope of the dose-response curve at low dose). The simplest hypothesis is that for different species, the ratio of carcinogenic potencies is constant for different materials, so that if material A is twice as potent a carcinogen as material B in species 1, it will also be twice as potent as material A in species 2. This is the idea of constant relative potency, as applied to carcinogenesis, and it underlies the standard approaches to estimating human risks from animals.

There is even some data which supports this idea! There have been several hundred bioassays performed simultaneously on rats and mice, and when the results of these are parametrized using a dose-response relationship which includes a linear term, we can estimate the potency in two species for each material tested. Plotting the potency measured in rats versus the potency measured in mice for each material then gives the figure shown. Notice that each measurement is uncertain to greater or lesser degree, due to the relatively small numbers of animals tested. If the idea of constant relative potency were exactly correct, these points would all lie on a straight line on the figure - or at least, all would lie sufficiently close to such a line that the measurement uncertainty bars on each point would encompass the line. From the figures, one can see that:

- (1) On average, potency in one species is proportional to potency in the other species.
- (2) There is a large scatter of the points around the lines of exact proportionality a scatter bigger than would be expected from the measurement errors alone.

A similar comparison can be attempted between the potencies measured in animal experiments, and those observed in humans. These cases have arisen in the past where humans have been exposed to materials before they were known to be carcinogenic. We can make use of other's misfortune to estimate how potent each such material is in humans, and compare with estimates obtained for mice and rats in laboratory experiments. In this case, the uncertainties are so large that little can be quantitatively states, although qualitatively the idea of constant relative potency does not seem to be disproved. A more recent and much more thorough study of comparisons between humans and animals has been carried out for the E.P.A. by Dr. Kenny Crump, and we can expect that to be published soon - I understand that conclusions are qualitatively similar.

9. Interspecies comparisons - practical and theoretical

The measure of carcinogenic potency introduced above was roughly defined as the ratio of (excess tumor probability)/(dose), at low enough dose. For the E.P.A. model usually used in risk assessments:

$$p = 1 - exp\{ - (q_0 + q_1.d + q_2.d^2 + ... + q_{k-1}.d^{k-1}) \}$$

the corresponding measure is q_1 . When this dose-response relationship is used with real data, it is usual to use an "upper 95% confidence limit" estimate q_1 * of q_1 as the measure of potency, since such an estimate is always non-zero (while, for example, the maximum likelihood estimate is often zero). The "upper 95% confidence limit" is with respect to the numerical uncertainties of the experiment only, and so this estimate of potency is in no sense an upper limit with respect to all the other uncertainties involved.

To compare humans with animals, the approach taken is to use a similar dose-response relationship in both cases:

Animal Human
$$p = 1 - exp\{ - (q_0 + q_1.d + ...) \}$$
 $p = 1 - exp\{ - (Q_0 + Q_1.D + ...) \}$

and then the constant relative potency hypothesis suggests that \mathbf{Q}_1 is proportional to \mathbf{q}_1 , or to our estimate \mathbf{q}_1^* of it:

$$Q_1 = const. q_1*$$

where the constant depends only on which animals species is used. We expect the constant to be different for different animal species - it will presumably depend on how we measure dose, on the relative lifespans of animal and human, on relative metabolic rates, and a whole host of other factors. With enough experiments, we could measure the constant in this relationship - at least in comparing animal with animal, rather than human with animal - and (in theory) empirically determine how it varies with these factors. The graphs above suggest that the constant is not completely constant, but that there is some sort of random uncertainty built in (or at least, an uncertainty that we can treat as random), amounting to an average factor of about 5.

If we are very lucky, it may be possible to find some way of measuring dose so that the constant in the above relationship is numerically equal to 1, so that the potency is equal in different species (up to the uncertainties) - just as it was possible to find such a measure in the case of the LD_{50} .

In practice, the E.P.A. <u>assumes</u> that the constant is exactly unity if the dose is measured as a (daily average amount)/(surface area of animal), by analogy with the LD_{50} case. (The graphs shown above actually suggest that it would be better to assume an average factor of unity, with an uncertainty factor of about 5, when the dose is measured as a (daily average amout)/(bodyweight of animal)).

10. An example - 1,2 Dibromoethane

As an example of the procedures usually adopted, let us look at the case of 1,2-Dibromoethane. What follows is by now means complete, but it indicates the sort of analysis which has to be performed. This example is confined to analysing just one result out of many, in a single bioassay (of about 5). In practice, it is essential to look at all the results.

The bioassay I have chosen was an inhalation bioassay in the National Toxicology Program series. A summary of the study design is:

Initial

| | number of animals | Concentration ppm (6 hrs/d, 5 d/wk) | • | study observed eks) |
|-------------|-------------------|-------------------------------------|-----|---------------------------|
| Male rats | | | | |
| control | 50 | 0 | 0 | 104-106 |
| low-dose | 50 | 10 | 103 | 1 |
| high-dose | 50 | 40 | 88 | 0-1 |
| Female rats | | | | |
| control | 50 | 0 | 0 | 104-106 |
| low-dose | 50 | 10 | 103 | 1 |
| high-dose | 50 | 40 | 91 | 0-1 |

And similarly for mice

We will look only at the results in female rats. First, their survival was not as good as might be desired in such an experiment, but the early mortality was probably due to the cancers appearing in the study, so it is acceptable - we can use (at least initially) the simplest analysis based on "end-of-life" data, without having to worry too much about the age dependence (this should always be backed up by further analysis, of course).

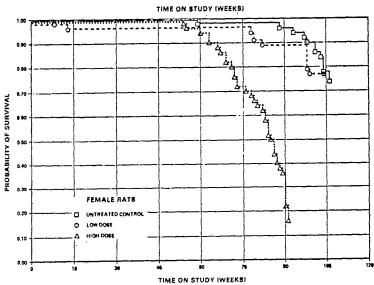


Figure 2. Survival Curves for Rats Exposed to Air Containing 1, 2-Dibromoethane

Tumors were found in many tissues. A summary of those tissues where more than 5% of the animals in any group were found with tumors is (for female rats):

| Subcutaneous tissue: fibroma | Control 0/50 | Low 0/50 | High 3/50 |
|---|-----------------|-------------|--------------|
| Subcutaneous tissue: fibroma | | | |
| or fibrosarcoma | 0/50 | 0/50 | 4/50 |
| Nasal Cavity: Carcinoma, NOS | 0/50 | 0/50 | 25/50 |
| Nasal Cavity: Sqamous cell carcinoma | 1/50 | 1/50 | 5/50 |
| Nasal Caavity: Adenoma, NOS | 0/50 | 11/50 | 3/50 |
| Nasal Cavity: Adenocarcinoma, NOS | 0/50 | 20/50 | 29/50 |
| Nasal Cavity: Adenomatous Polyp, NOS | 0/50 | 5/50 | 5/50 |
| Nasal Cavity: Papillary Adenoma | 0/50 | 3/50 | 0/50 |
| Nasal Cavity: Adenoma, NOS; Carcinoma, NOS; | | | |
| Adenocarcinoma, NOS; | | | |
| Papillary Adenoma; Adenomatous | s | | |
| polyp,NOS; and Sqamous cell | | | |
| Carcinoma | 1/50 | 34/50 | 43/50 |
| Lung: Alveolar/Bronchiolar Carcinoma | 0/50 | 0/48 | 4/47 |
| Lung: Alveolar/Bronchiolar Carcinoma or | | | |
| Adenoma | 0/50 | 0/48 | 5/47 |
| Hematopoietic System: All leukemias | 6/50 | 7/50 | 1/50 |
| Hematopoietic System: Monocytic leukemia | 6/50 | 5/50 | 1/50 |
| Circulatory System: Hemangiosarcoma | 0/50 | 0/50 | 5/50 |
| Circulatory System: Hemangiosarcoma or | | | |
| Hemangiosarcoma, invasive | • | 0/50 | 5/50 |
| Liver: Neoplastic nodule | 2/50 | 0/49 | 3/48 |
| Liver: Hepatocellular carcinoma | 0/50 | 1/49 | 3/48 |
| Liver: Neoplastic nodule or Hepatocellular | | | |
| carcinoma | 2/50 | 1/49 | 5/48 |
| Pituitary: Adenoma, NOS | 1/50 | 18/49 | 4/45 |
| Pituitary: Chromophobe adenoma | 20/50 | 0/49 | 0/45 |
| Adrenal: Pheochromocytoma | 3/50 | 1/49 | 0/47 |
| Thyroid: C-cell Carcinoma | 1/49 | 3/48 | 1/45 |
| Mammary Gland: Adenocarcinoma, NOS | 1/50 | 0/50 | 4/50 |
| Mammary Gland: Fibroadenoma | 4/50 | 29/50 | 24/50 |

Notice especially the various groupings which are employed - this is a matter of judgement. It is clear that the major effect is in the nasal cavity, but observe also the effect on fibroadenomas in the mammary gland, and the negative trend seen in the pituitary. Such negative trends are ignored.

Using the combined results in the nasal cavity, we fit the E.P.A. multistage model and find best estimates of:

$$q_0 = 2.699 \times 10_{-2}$$
; $q_1 = 6.876 \times 10^{-2}$; $q_2 = 0$;

and obtain an upper confidence limit for q_1 of $q_1*=8.6 \times 10_{-2}$ in all cases using as doses the values 0, 10 and 40 from the experimental design. In fact, the earlier figure of a distribution of values for q_1 is taken from this example - you can read the probability of q_1 being less than any given value from that figure.

Now what do we do with this estimate? That depends on the application, but we will assume that we wish to make a "UNIT RISK" estimate for humans from it - that is, estimate the lifetime risk to a human exposed to 1 microgram/ m^3 of dibromoethane for life.

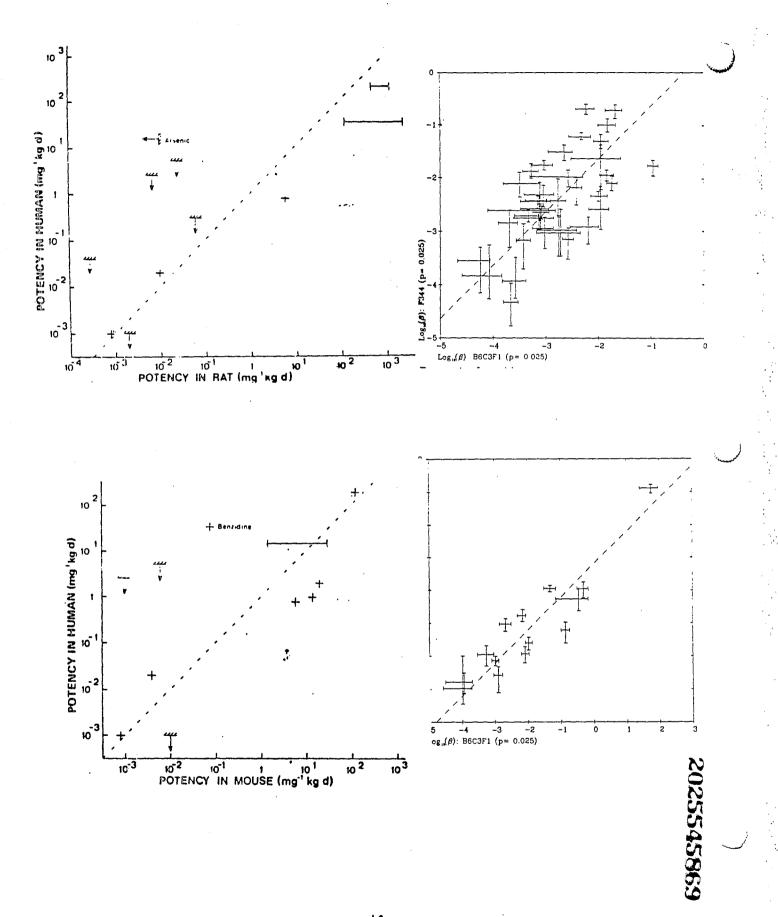
There are several extrapolations required. First, the animals were dosed for a lifetime, but not continuously. Correcting for continuous exposure introduces a factor of $7/5 \times 24/6$ (for days/week and hours/day) - but notice the subtle assumptions being made here, that it is average exposure that matters (and not peak exposure, for example).

Now we estimate that a female rat will suffer and increased lifetime risk of about 0.48 per ppm in the air (we assume that we are talking about such low doses that the excess risk is small). 1 ppm for 1,2-dibromoethane corresponds to about 7.6 mg/m 3 (one would estimate a little higher from the perfect gas laws), or 7600 microgram/m 3 , so that the increased lifetime risk to a female rat exposed continuously to 1 migrogram/m 3 is about 6.3 x 10 $^{-5}$

What about humans? We saw before that the assumption made was that humans are just as sensitive as animals - i.e. they suffer equal lifetime risks - if exposed at doses which are equal on an (amount)/(surface area) basis. Now it turns out that, approximately, equal concentrations in air lead to exposures which are equivalent on this basis, provided the species under consideration absorb about the same amount from the air they breathe. Thus the extrapolation to humans is simple in this case - one simply takes the same value for humans - a "UNIT RISK" of about 6.3 x 10^{-5} (i.e. that is the lifetime risk from continuous exposure to 1 migrogram/m³ of dibromoethane in the air).

It may be desired to estimate from this the effect on humans of ingestion of dibromoethane. In this case there are actually other bioassays in which dibromoethane was fed to animals under various conditions, but suppose that we have to make some estimate from the inhalation data. The "standard" human inhales, on average, about 20 m³ of air per day, and so inhales about 20 microgram/day of contaminant from air contaminated with 1 microgram/m³. If we assume that 100% of this contaminant is absorbed, the human's daily dose is 20 micrograms/day, or about 20/70 microgram/kg-day (as a fraction of bodyweight), or 2.9 x 10^{-4} mg/kg-day in the conventional units used. This results in a risk of about 6.3 x 10^{-5} , as detailed above, so that the potency is just the ratio of these -- 0.22 $(mg/kg-day)^{-1}$.

These short outline calculations have made several assumptions which require examination in any particular case. We have not looked at all the bioassay results, so one cannot expect that the numbers obtained here will correspond with what anybody else, who has done a more thorough job, will obtain -- they are placed here in order to show in outline what is done. In practice, one has to decide that the tumor site and type combinations are appropriate for combination in the animal species. That these tumors are relevant end points for estimating the probable effects on humans. That the route of administration, and method of administration are reasonable to produce results that may be extrapolated to humans. And a myriad of other details which have only been lightly touched upon, or completely omitted, in this sketch.



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TABLE E3. ANALYSIS OF PRIMARY TUMORS IN MALE MICE (Continued)

| | Vehicle | 500 | 1,000 |
|---|--------------------|--------------------|--------------------|
| | Control | mg/kg | mg/kg |
| Circulatory System: Hemangiosarcoma | | | |
| Overall Rates (a) | 4/50 (8%) | 3/49 (6%) | 1/50 (2%) |
| Adjusted Rates (b) | 10.1% | 8.8% | 2.6% |
| Terminal Rates (c) | 3/38 (8%) | 2/33 (6%) | 1/39 (3%) |
| Life Table Tests (d) | P=0.130N | P=0.559N | P=0.169N |
| Incidental Tumor Tests (d) | P=0.097N | P=0.408N | P=0.176N |
| Cochran-Armitage Trend Test (d) | P=0.134N | | |
| Fisher Exact Tests | | P=0.512N | P=0.181N |
| Circulatory System: Hemangioma or He | mangiosarcoma | | |
| Overall Rates (a) | 4,50 (8%) | 4/49 (8%) | 1/50 (2%) |
| Adjusted Rates (b) | 10.1% | 11.8% | 2.6% |
| Terminal Rates (c) | 3/38 (8%) | 3/33 (9%) | 1, 39 (3%) |
| Life Table Tests (d) | P=0.142N | P=0.579 | P=0.169N |
| Incidental Tumor Tests (d) | P=0.110N | P=0.573N | P=0.176N |
| Cochran-Armitage Trend Test (d) | P=0.147N | 1 -0.575.4 | 1 -0.170.1 |
| Fisher Exact Tests | 1-0.14714 | P=0.631 | P=0.181N |
| | | 1 -0.031 | 1 -0.101.1 |
| Liver: Adenoma | 0.50 (00) | £:40 (10°) | 12 50 /2/01 |
| Overall Rates (a) | 0/50 (0%) | 5 49 (10%) | 13,50 (26%) |
| Adjusted Rates (b) | 0.0% | 13.0% | 33.3% |
| Terminal Rates (c) | 0/38 (0%) | 3/33 (9%) | 13/39 (33% |
| Life Table Tests (d) Incidental Tumor Tests (d) | P<0.001 P<0.001 | P=0.030 P=0.023 | P<0.001 P<0.001 |
| Cochran-Armitage Trend Test (d) | P<0.001 | 1-0.02, | 1 < 0.001 |
| Fisher Exact Tests | F<0.001 | P=0.027 | P<0.001 |
| | | F-0.027 | 1 < 0.001 |
| Liver: Carcinoma | 10.50.42000 | 14 40 40000 | 12 50 (245) |
| Overall Rates (a) | 10/50 (20%) | 14, 49 (29%) | 12 50 (24%) |
| Adjusted Rates (b) | 24.3% | 35.9% | 25.8% |
| Terminal Rates (c) | 7, 38 (18%) | 9 33 (27%) | 5/39 (13%) |
| Life Table Tests (d) | P=0.427 | P=0.183 | P=0.463 |
| Incidental Tumor Tests (d) | P=0.536 | P=0.379 | P=0.548N |
| Cochran-Armitage Trend Test (d) | P=0.363 | D-0.004 | D-0.40¢ |
| Fisher Exact Tests | • | P=0.224 | P=0.405 |
| Liver: Adenoma or Carcinoma | 10.50 (200) | 10 10 13 20 1 | 23 52 445 |
| Overall Rates (a) | 10 50 (20%) | 18 49 (37%) | 23 50 (46% |
| Adjusted Rates (b) | 24.3% | 45.1% | 49.8% |
| Terminal Rates (c) | 7 38 (18%) | 12 33 (36%) | 16 39 (41% |
| Life Table Tests (d) | P=0.013 | P=0.042 | P=0.014 |
| Incidental Tumor Tests (d) | P=0.009 | P=0.098 | P=0.019 |
| Cochran-Armitage Trend Test (d) | P=0.004 | D 0.050 | D 000# |
| Fisher Exact Tests | | P=0.052 | P=0.005 |
| Forestomach: Squamous Cell Papilloma | | | |
| Overall Rates (a) | 3 49 (6%) | 3 48 (6%) | 9 49 (18%) |
| Adjusted Rates (b) | 7.9% | 9.1% | 23.1% |
| Terminal Rates (c) | 3 38 (8%) | 3 33 (9%) | .9 39 (23%) |
| Life Table Tests (d) | P=0.038 | P=0.597 | P=0.065 |
| Incidental Tumor Tests (d) | P=0.038 | P=0.597 | P=0.065 |
| Cochran-Armitage Trend Test (d) | P=0.034 | | |
| Fisher Exact Tests | | P=0.651 | P=0.060 |

TABLE B3.

INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE IN THE 2-YEAR STUDY OF BENZYL ACETATE

HIGH DOSE

| ANIMAL Number | 21 | 21 | 21 | 21 | 31 | 3 | 31 | 3 | 3 | 31 | 3 | 31 | 31 | 3 | 4 | 1 | 21 | 31 | 4 | 5 | 4 | <u>-} </u> | 4 | 4 | 5 | TOTAL TISSUES |
|--|--|----------|----------|----------|----------|----------|----------|----------|------------|----------|----------|----------|----------|----------|----------|----------|--|------------|------------|----------|------------|------------|----------|----------|----|------------------|
| HEEKS OH Study | 9 | į | | • | 1 | - | 0 | 2 | 01 | 9 | 1 | 01 | 81 | - | 11 | | 71 | 21 | 01 | 11 | 91 | 11 | 100 | 31 | 1 | TISSUE TUXOR |
| RESPIRATORY SYSTEM | 1-7 | -21 | -2! | -31 | | -21 | -21 | - 21 | . 21 | - 61 | -21 | -21 | -21 | -21 | -12 | 31 | 21 | 31 | ğΙ | .21 | 31 | 21 | 51 | 21 | -7 | |
| LUNGS AND BRONCHI MEPATOCELLULAR CARCINONA, METAS ALVEDLAR/BRONCHIOLAR ADENOMA ALVEDLAR/BRONCHIOLAR CARCINOMA | + | + | + | + | • | + | • | • | * x | • | • | * | • ` | | * X | ٠ | • | ÷ Ž | * | + | • | + | ٠ | + | ٠ | 50 1 6 |
| TRACHEA | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | - | + | + | + | + | + | + | 49 |
| HEMATOPOIETIC SYSTEM | _ | | | | _ | | | | | _ | _ | | | | _ | _ | _ | | | _ | | _ | | | + | |
| BONE MARRON | - | <u> </u> | ٠ | + | * | * | + | + | + | <u>*</u> | <u>+</u> | * | <u>+</u> | ÷ | <u>*</u> | ٠ | <u>+</u> | + | + | <u>+</u> | + | + | + | ۰ | | 50 |
| SPLEEN HEMANGIOSARCOMA | - | + | + | <u>+</u> | <u>+</u> | <u>.</u> | <u>.</u> | * | • | + | + | * | <u>.</u> | <u>.</u> | + | + | + | + | - | + | + | + | + | + | * | 49, |
| LYMPH HODES HALIGNANT LYMPHOMA, MIXED TYPE | <u> -</u> | + | + | + | + | + | _ | + | + | * | <u>+</u> | <u>+</u> | + | + | + | • | + | + | + | + | + | + | + | + | ٠ | 58 |
| THYMUS | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | | + | + | + | 49 |
| CIRCULATORY SYSTEM | - | | | | _ | - | | | _ | - | | - | | - | | | | | | | | | | | + | |
| HEART | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| DIGESTIVE SYSTEM | \vdash | | _ | | | | | _ | _ | | | | | | _ | _ | _ | | _ | | _ | _ | | | + | |
| SALIVARY GLAND | - | ٠ | ٠ | ٠ | + | + | * | • | + | +. | + | ٠ | ٠ | <u>*</u> | <u>.</u> | +_ | <u>*</u> | ٠ | + | +_ | ٠ | + | ÷ | | + | 49 |
| LIVER NEOPLASH, NOS HEPATOCELLULAR ADEHOMA | + | + x | + | + x | + | + | * | + | + x | ٠ | + | + | + | + | | + x | | * X | | + x | + | + | + ¥ | + | * | 58 1 |
| HEPATOCELLULAR CARCINOMA | _×_ | _ | | | | | _ | _ | _ | χ. | X. | | | | _ | Ž_ | X_ | | Χ. | _ | | | _ | | 7 | 12 |
| BILE DUCT | 1- | <u> </u> | <u>.</u> | + | * | <u>.</u> | • | + | + | <u>+</u> | <u>+</u> | +_ | * | ٠ | <u>.</u> | + | +_ | + | ٠ | <u>*</u> | ٠. | + | ٠ | <u>+</u> | + | 50_ |
| GALLBLADDER & COMMON BILE DUCT | - | +. | • | * | ٠ | +. | + | ×. | +_ | + | + | ٠ | + | ٠_ | <u>.</u> | <u>*</u> | <u>.</u> | <u>+</u> | ¥ | <u>+</u> | <u>+</u> | <u>+</u> | ÷ | <u></u> | 4 | 50× |
| PANCREAS | + | * | * | <u>.</u> | * | <u>+</u> | ÷ | * | +_ | + | <u>*</u> | <u></u> | + | <u>.</u> | * | * | * | <u>+</u> | - | * | <u>+</u> | <u>+</u> | <u>*</u> | ٠ | 솩 | 49 |
| ESOPHAGUS | - | <u> </u> | <u> </u> | <u> </u> | <u></u> | + | * | * | <u>*</u> | ÷ | <u>.</u> | + | * | ٠ | <u>.</u> | +_ | ٠. | + | =_ | <u>*</u> | <u>*</u> | <u>*</u> | ۰ | - | 4 | 48 |
| STOMACH SQUAMOUS CELL PAPILLOMA SQUAMOUS CELL CARCINOMA | Ŀ | • | • | * | ż | <u> </u> | <u> </u> | * | * * | • | • | + | ž | • | ž | ż | • | • | • | + | * | * | + | + | + | 49 ₉ |
| SMALL INTESTINE | <u> </u> | + | ٠ | ٠ | ٠ | ٠ | ٠ | - | ٠ | ٠ | + | ٠ | <u>*</u> | ٠. | + | | ٠. | | _ | <u>.</u> | <u>.</u> | <u>+</u> | ٠ | ٠ | + | 47 |
| LARGE INTESTINE URINARY SYSYEM | ŀ | + | <u>+</u> | <u>.</u> | + | <u>.</u> | <u>.</u> | + | <u>.</u> | _ | ٠ | <u>.</u> | + | <u>.</u> | <u>.</u> | ٠_ | ٠ | • | | + | • | • | • | ٠ | + | 46 |
| KIDHFY | ١. | | | | ٠ | | | | ٠ | | | | | _ | | | | | | | ٠ | | | | + | 50 |
| TUBULAR-CELL ADENOMA TUBULAR-CELL ADENOCARCINOMA | <u> </u> | <u>.</u> | | | | _ | | | · <u> </u> | _ | _ | _ | _ | _ | ž | _ | _ | _ | _ | _ | _ | _ | _ | _ | 1 | |
| URTHARY BLADDER | 1 + | + | * | + | + | * | + | + | ٠ | * | + | + | + | ٠ | + | + | + | + | • | * | + | + | + | + | + | 49 |
| ENDOCRINE SYSTEM | Г | | | | | | | | | | | | | | | _ | _ | | | | | _ | _ | | 7 | |
| PITUITARY | <u> </u> + | * | <u> </u> | <u> </u> | * | + | <u></u> | <u>+</u> | + | * | <u></u> | <u>+</u> | ÷ | ÷ | ÷ | <u>*</u> | <u>+</u> | <u>.</u> | - | <u>.</u> | <u>*</u> _ | * | <u>+</u> | * | * | 46 |
| Adrenal Ganglioneuroma | <u> -</u> | <u></u> | <u>+</u> | ÷ | + | <u>.</u> | <u></u> | <u>.</u> | + | <u>+</u> | <u>+</u> | <u>+</u> | <u>.</u> | <u>+</u> | | | _ | <u>+</u> _ | _ | | | + | + | <u>+</u> | * | 49, |
| THYROID FOLLICULAR-CELL ADENOMA | <u> </u> | ż. | _ | ž. | <u>.</u> | * | * | + | <u>.</u> | <u>+</u> | * | * | * | * | <u>.</u> | * | <u>+</u> | + | _ | <u>*</u> | * | * | + | • | -1 | 47 |
| PARATHYROID | 1. | + | * | | + | + | + | ٠ | • | + | + | + | + | - | | + | <u>. </u> | + | _ | | _ | + | | - | + | 44 |
| PANCREATIC ISLETS ISLET-CELL ADENOMA | + | + | + | + | + | + | + | + | ٠ | + | + | + | + | + | + | + | + | • | - | + | + | + | * | ٠ | + | 472 |
| REPRODUCTIVE SYSTEM | | _ | - | _ | - | | _ | _ | | _ | _ | _ | | _ | _ | _ | | - | | _ | - | | | | + | |
| HAPPLARY GLAND | Н. | ×. | Ħ | H | × | н | Ħ | H | Ħ | × | H | н | H | Ħ. | Ħ | M | н | × | * | × | H. | N. | H. | N. | N. | 50× |
| TESTIS INTERSTITIAL-CELL TUMOR | + | ţ | • | + | + | <u>.</u> | • | + | * | + | <u>.</u> | <u>.</u> | <u>.</u> | + | + | + | + | + | + | <u>.</u> | <u>*</u> | + | * | + | + | 58 2 |
| PROSTATE MERVOUS SYSTEM | <u> </u> | <u>+</u> | ÷ | * | * | + | <u>*</u> | <u>.</u> | <u>*</u> | +_ | <u>*</u> | <u>+</u> | • | <u>.</u> | <u>*</u> | + | <u>+</u> | <u>+</u> | - | <u>+</u> | + | * | +_ | + | + | 49 |
| BRAIN | | + | | + | + | + | + | + | + | + | + | | + | + | + | | + | + | + | + | | + | | + | + | 50 |
| SPECIAL SENSE ORGANS | - | | | | | _ | _ | _ | _ | _ | _ | _ | _ | - | _ | _ | _ | _ | | _ | _ | _ | | _ | + | |
| HARDERIAN GLAND ADENOMA, NOS | × | × | H | N | Ħ | H | ĸ | Ħ | × | H | × | × | × | × | × | × | × | × : | X | × | × | × | × | × | × | 50× |
| ODY CAVITIES | - | | | | | _ | | _ | | - | - | | - | | | | | | | | | | | | + | |
| MESENTERY HEPATOCELLULAR CARCINOMA, METAS | * | ĸ | × | Ħ | Ħ | × | H | H | × | × | × | × | × | H | Ħ | H : | N : | H : | ie. | H | H | H | H | × | × | 50× |
| ALL OTHER SYSTEMS | | | | | | _ | _ | | _ | | _ | _ | _ | | | | - | _ | | - | _ | _ | _ | | + | |
| MULTIPLE ORGANS NOS HEPATOCELLULAR CARCINOMA, METAS MALIGHATI LYMPHOMA, NOS HALIGLYMPHOMA, LYMPHOCYTIC TYP | H | × | H | H | ĸ | × | H | × | Ħ | × | × | × | × | x | H | н : | н : | H | 3 2 | H | × | × | × | × | × | 50× |

* ANIHALS NECROPSIED

- +: TISSUE EXAMINED MICROSCOPICALLY
 -: REQUIRED TISSUE NOT EXAMINED MICROSCOPICALLY
 X: TUMOR INCIDENCE
 H: HECKOPSY, NO AUTOLYSIS, NO MICROSCOPIC EXAMINATION
 S: ANIMAL MIS-SEEDS

ETC.

2025545872

How Do Cancer Risks Predicted From Animal Bioassays Compare with the Epidemiologic Evidence? The Case of Ethylene Dibromide

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Cancer risks for ethylene dibromide (EDB) were estimated by fitting several linear non-threshold additive models to data from a gavage bioassay. Risks predicted by these models were compared to the observed cancer mortality among a cohort of workers occupationally exposed to the same chemical. Models that accounted for the shortened latency period in the gavaged rats predicted upper bound risks that were within a factor of 3 of the observed cancer deaths. Data from an animal inhalation study of EDB also were compatible with the epidemiologic data. These findings contradict those of Ramsey et al. (1978), who reported that extrapolation from animal data produced highly exaggerated risk estimates for EDB-exposed workers. This paper explores the reasons for these discrepant findings.

KEY WORDS: Ethylene dibromide; risk assessment; cancer; occupational exposure.

1. INTRODUCTION

In the absence of adequate human data, quantitative cancer risk assessments have relied heavily on extrapolations from animal bioassays conducted at comparatively high doses. (1) The validity of such extrapolations has, however, been a source of controversy. (12-8) A case in point is that of ethylene dibromide (EDB), a fumigant that, until recently, was widely used on grain and citrus products. Results of an animal bioassay (9) showed EDB to be an extremely potent carcinogen when administered by gavage. For regulatory purposes, the Carcinogen Assessment Group (CAG) of the U.S. Environmental Protection Agency used these bioassay data to estimate human risks from consumption of EDB residues in food. (10,11)

Ramsey and associates⁽²⁾ applied the risk extrapolation model used in an early report of the regulatory agency⁽¹⁰⁾ to a cohort of workers at two chemical manufacturing plants who were exposed to EDB by inhalation, and whose mortality was under study.⁽¹²⁾ The results of Ramsey et al. suggested a wide discrepancy between the observed mortality and the risks predicted from the animal gavage data by a low-dose-linear extrapolation model. These results have been cited as evidence that extrapolations from animal bioassays to human real-world exposures are implausible and hence contraindicated.^(2-6,13)

In this paper we investigate the reasons for the apparent discrepancy. Other nonthreshold models which are linear at low doses are fitted to the gavage data, including the one used in the final risk assessment of the CAG. (11) Models are also fitted to data from a more recent inhalation bioassay. (14) The use of safety factors is not considered because of the limitations of this approach. (15) We then apply each fitted model to the cohort of EDB-exposed workers

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²California Department of Health Services, Berkeley, California 94704.

and compare the predicted risks to the observed cancer mortality.

2. THE EDB DATA AND THE REPORTED DISCREPANCY

Cancer deaths among workers exposed to EDB were reported as not significantly elevated, unless a small group with additional exposure to arsenic was included.(12) However, in a long-term gavage bioassay, (9) and in two inhalation studies (14,16) published subsequent to the risk assessment of CAG, EDB proved highly carcinogenic. In the two assays (one gavage and one inhalation) conducted by the National Cancer Institute/National Toxicology Program (NCI/NTP), more than 50% of the high-dose animals exhibited contact-site tumors (squamous cell carcinomas of the stomach from gavage administration, nasal cavity malignancies of several types from inhalation). Both low- and high-dose animals had statistically significant excesses of contact-site tumors and a variety of tumors remote from the site of administration (i.e., systemic tumors).

A one-hit, nonthreshold model was fitted by the CAG (10) to the rat data from the NCI gavage bioassay to assess risk from ingestion of EDB-contaminated food. The CAG used squamous cell carcinomas of the stomach in male rats and an interspecies conversion based on surface area equivalence. In developing its risk assessment for public exposure via ingestion, the CAG specified that the parameter estimates were applicable only for intubation exposure. Different parameter estimates were recommended for dietary exposure and for inhalation exposure (10) (in a later risk assessment of EDB, the CAG scientists developed a more sophisticated model to deal with the irregularities in the gavage bioassay (11)).

Ramsey et al.⁽²⁾ applied the one-hit model fitted by the CAG to a cohort of 161 employees involved in the manufacture of EDB.⁽¹²⁾ Exposure was estimated by (i) assuming all workers were exposed to time-weighted average (TWA) concentrations based on measurements made during the 1970s at one of the two plants,⁽¹²⁾ and (ii) converting to a continuous lifetime equivalent dose using an average weight of 70 kg. Additionally, it was assumed that both potency and biologically effective dose were the same for inhalation as for intubation, i.e., no adjustments were made for route of exposure.

The risk of an EDB-induced cancer death was calculated for each worker in the study by Ott et al. These were then summed to obtain the number of excess cancer deaths predicted by the model. In the cohort of 161 workers, this model predicted over to excess cases of cancer from an exposure of 3.0 ppm, or about 50 cases from 0.9 ppm exposure. (2) These predictions are for the partial lifetimes of the workers. Given that only eight cancer deaths were observed, with a 95% upper bound of 16, these predictions are clearly inconsistent with the observed mortality.

Figure 1a displays a comparison of (a) observed cancer deaths, (b) expected cancer deaths based on U.S. white male age-specific rates, and (c) cancer deaths predicted by this model. Predictions are shown for each of the two assumed exposure levels. Since measurements were taken at the Michigan plant only, results for the two plants are presented separately.

In light of this discrepancy between predicted and observed cancer mortality in EDB-exposed workers, some authors have suggested that extrapo-

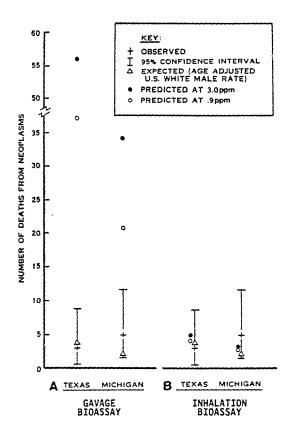


Fig. 1. Observed, expected, and predicted cancer deaths using one-hit model and two animal bioassays of ethylene dibromide.

lating from animal bioassay data to predict human cancer risks is inappropriate. (3-6) Because data from such assays are often the strongest evidence of carcinogenicity and usually the only basis available for quantification of human risks, alternative explanations should be investigated before drawing such a conclusion. These should include the possibilities that the assumed exposures in the occupational study were too high, that some aspect of the model or its application to the workers was inappropriate, or that the method for scaling doses between species was incorrect.

It seems unlikely that the workers' exposures were greatly overestimated. Most of the exposures to EDB occurred decades before the measurements were taken, suggesting underestimation of exposure. While individual work histories or job activities were not taken into account, and while it is possible that heavily exposed short-term workers were excluded and that long-term employees experienced lower exposures than the TWAs, biases due to these factors are likely to be less significant than the changes in exposure over time. With risk predictions over sevenfold too high (even using the lower of two estimated TWAs), inaccuracies in exposure assessment are unlikely to explain the inconsistency between observed and predicted cancer deaths. We have therefore explored other potential explanations: deficiencies of the model, problems in its application to the workers including the different route of exposure, and the interspecies conversion factor.

3. METHODS AND RESULTS

A crude extrapolation using direct proportionality from the lowest dosed animals in the gavage experiment indicated compatibility between the animal and occupational data. The low-dose gavaged rats received 5.37 mg/kg/day (in human equivalent) and developed 60% more tumors than the control rats. The average worktime dose in the occupational study was 4.6 mg/kg/day, which amounts to only 0.35 mg/kg/day when averaged over their lives. This represents about 0.065 of the rats' dose, implying an excess risk of 0.04 for each worker (0.065×0.6), or about six extra cancer deaths in the cohort of 161, where three excess cancer deaths were seen.

We further compared the observed cancer deaths among workers in the study by Ott et al. (12) with predictions from several linear nonthreshold models,

using data from both the NCI inhalation bioassay (14) and the NCI gavage bioassay. (9) The following models were used: the one-hit model and the multistage' model were fitted to the inhalation bioassay data; the multistage model incorporating time-to-tumor data, the multistage model with variable dosing, and the proportional hazards model were fitted to the gavage data. In each case the fitted extrapolation model was applied to the workers' exposure to obtain predicted cancer risks, which were then compared with observed cancer deaths in the EDB-exposed cohort. For the inhalation bioassay, nasal cavity malignancies in male rats represented the most sensitive site, sex, and species. To simplify comparison, we made the same exposure assumptions as Ramsey et al., (2) with the exception that the model incorporating variable dosing and the Cox model do not assume that average lifetime dose is the determinant of risk. Also, while CAG used data from only the low-dose animals in the gavage study, these analyses used data from all dosed animals.

3.1. Inhalation Data: Two Models

The one-hit, nonthreshold model takes the form

$$P(d) - P(0) = 1 - \exp(-\beta \cdot d)$$

where P(d) represents average lifetime cancer risk for an individual exposed to dose d, P(0) is the background lifetime cancer risk, and β is the unknown parameter for carcinogenic potency (i.e., mortality per unit dose) of the substance. When fitted to the inhalation bioassay data using Global 82 software, (17) this model predicted upper limits of 1.2 and 0.7 excess cancer deaths among the exposed workers at the Texas and Michigan plants, respectively, assuming EDB concentrations averaged 3.0 ppm for all workers at both plants. Since the inhalation experiment ran for the full two years, and since most of the animals were sacrificed at term, the calculation of partial lifetime risks for the workers was based on the exponent for time (or age) dependence of cancer risk obtained from the gavage data. Other researchers have estimated similar values for the age dependence of human cancer (18,19); using smaller values as reported for lung cancer by Doll and Peto(20) did not substantially alter the results. As shown in Table I and Fig. 1b, when the small excess risks predicted by this model were added to the expected deaths, the resulting total predicted cancer

| Table I. | Numbers of Cancer Deaths Predicted by Linear Nonthreshold Models Fitted |
|---------------------------------|---|
| | to Inhalation Data |
| Here was a second succession of | |
| | Excess predicted ^b by one-hit model |
| | Wish sugar from A and a 1 1 1 m |

| | | | Excess predicted ^b by one-hit model | | | | | | | |
|-------------------|------------------------------|-----------------------|--|----------------------------|----------------------------|----------------------------|--|--|--|--|
| | Observed | Omitted | With tu | mors found a Inclu | t terminal sac ded | rifice: | | | | |
| ************* | (95% CI) | Expected ^a | 0.9 ppm | 3.0 ppm | 0.9 ppm | 3.0 ppm | | | | |
| Texas Michigan | 3° (0.6-8.8) 5 (1.6-11.7) | 3.6 2.2 | 0.13 ^d (0.17) ^e 0.08 (0.10) | 0.44 (0.57) 0.26 (0.33) | 0.30 (0.38) 0.17 (0.22) | 1.00 (1.25) 0.58 (0.72) | | | | |

From U.S. white male age- and calendar-year-specific mortality rates.

mortality was close to the observed mortality among the EDB-exposed workers.

The multistage model generalizes the one-hit model by allowing for nonlinear terms in the hazard rate of cancer death. This model is of the form

$$P(d) - P(0) \approx 1 - \exp[-(\beta_1 \cdot d + \beta_2 \cdot d^2 + \cdots)]$$

with β_i the unknown parameters. When fitted to the inhalation data, the linearized multistage model predicted identical risks, that is, the strong linearity in the data dictated that the best fit was the one-hit model.

3.2. Gavage Data: Three Models

The gavage bioassay was marked by severe early mortality from both toxic and carcinogenic effects of the high doses of EDB: one-third of the high-dose animals died by the 15th week. The two-year bioassay was, therefore, terminated before the end of the Hill part to subject for the shortened lifespains and Short camer latencies, a variation of the multistage model incorporating the survival times of the animals (denoted multistage with time-to-tumor model) was fitted to these data using Weibull 82 software. (21) The form of this model is

$$P(d) - P(0)$$
= 1 - exp[- (\beta_1 \cdot d + \beta_2 \cdot d^2 + \cdot \cdot)(t - t_0)^{\gamma}]

where t represents time since first exposure and t_0 represents the latency period. Thus, β_i and t_0 are parameters to be estimated. Using this model, the upper-limit predictions were two to three times the observed cancer deaths assuming exposures of 3.0 ppm: 11.9 and 3.9 excess cancer deaths at the Texas and Michigan plants, respectively.

In response to the early mortality, dosing was stopped for the high-dose animals, and subsequently a variable dosing pattern was instituted for this group. Zeise and Crouch, (22) Thorslund, (23) and Crump and Howe⁽²⁴⁾ developed a special case of the Armitage-Doll multistage model for carcinogenesis, which incorporated such a variable dosing regimen. This model was used in the CAG's final risk assessment for EDB.(11) and took the form

$$P(d) - P(0)$$

= $1 - \exp[-(\beta \cdot d)[(t - s)^{\gamma} - (t - f)^{\gamma}]]$

where s is the age at start of exposure, f is the age at end of exposure, t is the age at end of observation period, and d is the daily dose from age s to f. Y/lifit filled it, the garage data, this model gave predictions that were similar to those of the time-totumor model: 10.4 and 5.5 excess cancer deaths at the Texas and Michigan plants, respectively, assuming concentrations of EDB averaged 3.0 ppm (see Table II). Thus, a variable dosing schedule did not significantly influence the risk projections.

The Cox proportional hazards model differs from the previously described models by treating the increase in risk as a multiplicative rather than an additive effect. The model takes the form(25)

$$P(d,t) = 1 - \exp \left[-\int_0^t \lambda(d_u, u) \, \partial u \right]$$

^bModels were fitted to inhalation data using Global 82 software published by Crump and Howe (1982). Proportion with tumors was based on life table adjustment. Animals who died prior to the first tumor were not included.

^{&#}x27;Included one arteriosclerotic heart disease death with lymph node malignancy (see Ref. 2).

^dMaximum likelihood estimates.

Numbers in parentheses are upper 95% confidence limits.

Table II. Numbers of Cancer Deaths Predicted by Multistage Model Adapted for Variable Dosing Fitted to Gavage Data

| | Number of Cancer Deaths | | | | | | | | |
|----------|-------------------------|-----------------------|---------------------------------------|--------------|--|--|--|--|--|
| | Observed | | Excess predicted by mode | | | | | | |
| | (95% CI) | Expected ^a | 0.9 ppm | 3.0 ppm | | | | | |
| Texas | 3° (0.6-8.8) | 3.6 | 2.84 ^d (3.49) ^e | 8.65 (10.42) | | | | | |
| Michigan | 5 (1.6–11.7) | 2.2 | 1.95 (2.33) | 4.84 (5.53) | | | | | |

[&]quot;From U.S. white male age- and calendar-year-specific mortality rates.

where P(d, t) represents the risk by time = t, for a dosing pattern d, and $\lambda(d_u, u)$ represents the instantaneous hazard at time u due to dose $= d_u$ (= dose between 0 and u). Furthermore, this model assumes that the hazard for an exposed individual is proportional to the base-line hazard at all times:

$$\lambda(d,t) = f(d) \cdot \lambda(0,t)$$

(Dose can be a function of time or not.) This model has been used recently as a basis for developing and comparing potencies from animal carcinogenicity bioassays. (26-25) The function f(d) is taken to be linear: $(1+\beta \cdot d)$. The following steps implemented this model:

- a. The parameter β was estimated from the animal gavage data.
- b. For each worker j, the integrated base-line hazard, $H_i(0)$, was determined using age-,

- race-, sex-, and calendar-year-specific rates for U.S. males.
- c. The predicted excess probability of a cancer death for worker j at dose = d was derived using $H_j(0)$, the estimate for β , and the proportional hazards assumption:

$$P(d_j) + P(0) = 1 - \exp\left\{-\left[\beta d_j\right] \cdot \left[H_j(0)\right]\right\}$$

d. The predicted number of excess cancer deaths for the cohort was obtained by summing the risks over all workers in the cohort.

Unlike the previously discussed models, the Cox proportional hazards model assumes that the excess risk is a function of the background rates. Since EDB is not expected to affect all cancer sites uniformly, two potential sites were selected for extrapolation: lung and stomach.

The excess lung cancer deaths predicted by the Cox model assuming that EDB concentrations averaged 3.0 ppm were 46.8 and 22.1 for the Texas and Michigan plants, respectively; predicted excess stomach cancer deaths were 17.8 and 9.5. These predictions are maximum likelihood estimates; because of the strong monotonicity of the gavage data, the variance was too unstable to derive a reliable confidence interval. The high lung cancer predictions were similar to those of the one-hit model fitted to the gavage data.

Tables III and IV summarize the risk predictions from all of the models discussed above. For simplicity of presentation, Table III assumes 0.9 ppm exposure, and Table IV assumes 3.0 ppm exposure.

Table III. Total a Cancer Deaths Predicted by Several Models for EDB-Exposed Workers

| والمتارسية البرو منتري | | | | Models fitt | ed to gavage data | to the second to | | | | |
|------------------------|-----------------|--------------|---------|-------------|-------------------|--|------------------------------------|-------------------|--|--|
| | | Proportional | | | | | | o inhalation data | | |
| | Observed cancer | | hazar | ds | Multistage with | Multistage with | One-hit: terminal sacrifice tumor: | | | |
| | deaths | One-hit | Stomach | Lung | time-to-tumor | variable dosing | Omitted | Included | | |
| Texas | 3 | 38.6 | 10.4 | 31.4 | 7.7 | 7.1 | 3.8 | 4.0 | | |
| Michigan | 5 | 21.2 | 5.9 | 13.0 | 3.5 | 4.5 | 2.3 | 2.4 | | |
| Overall | . 8 | 59.8 | 16.3 | 44.4 | 11.2 | 11.6 | 6.1 | 6.4 | | |

^{*}Total cancer deaths = [expected + predicted excess].

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^hMultistage model adapted for variable dosing (Ref. 11).

^{&#}x27;Includes one arteriosclerotic heart disease death with lymph node rnalignancy (see Ref. 2).

^dMaximum likelihood estimates.

Numbers in parentheses are upper 95% confidence limits.

bOther assumptions are described in the text. Values in the table represent upper 95% confidence limits, except for the proportional hazards model. which the variance estimates were too unstable to derive an upper confidence limit.

^{&#}x27;Assumes 0.9 ppm exposure during time employed.

Table IV. For Total^a Cancer Deaths Predicted^b by Several Models for EDB-Exposed Workers^c

| أرهارها مدارها والمناود | | · |] | Models fitt | ed to gavage data | ar afasan Anton Callandon and a | | | | |
|-------------------------|-----------------|---------|---------|-------------|-------------------|---------------------------------|----------------------------------|------------------|--|--|
| | | | Proport | ional | | | Models fitted to | o inhalation dau | | |
| | Observed cancer | | hazar | ds | Multistage with | Multistage with | One-hit: terminal sacrifice tumo | | | |
| | deaths | One-hit | Stomach | Lung | time-to-tumor | variable dosing | Omitted | Included | | |
| Texas | 3 | 56.6 | 21.4 | 50.4 | 15.5 | 14.0 | 4.2 | 4.9 | | |
| Michigan | 5 | 34.2 | 11.7 | 24.3 | 6.1 | 7.7 | 2.5 | 2.9 | | |
| Overall | 8 | 90.8 | 34.5 | 74.7 | 21.6 | 21.7 | 6.7 | 7.8 | | |

[&]quot;Total cancer deaths = [expected + predicted excess].

Table V. Effect of Interspecies Dose Conversion Factor on Cancer
Risk Predictions^a

| | Dose equivalence by | | | | | | | |
|--------------------------------|---------------------|---------------------------|--|--|--|--|--|--|
| Predicted excess cancer deaths | mg/kg/day | mg/kg ^{2/3} /day | | | | | | |
| Texas | | | | | | | | |
| 0.9 pm | 0.8 | 4.1 | | | | | | |
| 3.0 ppm | 2.6 | 11.9 | | | | | | |
| Michigan | | | | | | | | |
| 0.9 ppm | 0.3 | 1.3 | | | | | | |
| 3.0 ppm | 0.8 | 3.9 | | | | | | |

[&]quot;Time-to-tumor model fitted to gavage data. Values in the table represent upper 95% confidence limits.

3.3. Interspecies Scaling Factor

As noted, the gavage analyses used surface area to scale the doses from animals to man. To investigate the role of the interspecies scaling factor we repeated the analysis that fitted the multistage with time-to-tumor model to the NCI gavage bioassay data, using mg/(kg body weight)/day equivalence rather than surface area equivalence. A comparison of these two analyses is shown in Table V. Surface area equivalence yielded risk estimates that were about five times larger than those based on mg/kg/day equivalence.

4. DISCUSSION

The large uncertainty in risk assessment due to extrapolating between high and low doses is of considerable concern. Unfortunately, the only feasible way to conduct a sensitive animal bioassay is to use high doses, since the risks at low doses generally

cannot be detected unless many thousands of animals are treated; nevertheless, such risks may be of considerable public health concern if exposures are widespread. Thus, the uncertainty of high-to-low dose extrapolation is unavoidable. One result of this investigation was to develop a means of narrowing the range of uncertainty by comparing model-based estimates derived from animal data to the observations in epidemiologic studies.

All the linear nonthreshold additive risk models considered here for extrapolating human cancer risks from animal bioassay data performed well when validated against the mortality of EDB-exposed workers. That is, the predictions are compatible with the reported cancer deaths in the occupational study of Ott and colleagues. (12) Even a crude extrapolation using direct proportionality, which is equivalent to drawing a straight line between zero excess risk at zero dose and the excess tumor rate in the low-dose rats, gave plausible risk estimates when compared to the epidemiologic data. This compatibility contrasts sharply with the findings of Ramsey and coworkers. (2) We discuss the reasons for this difference and the implications of our findings.

4.1. Choice of Model

On theoretical grounds, the multistage model for variable dosing and time-dependent risk appears to be the most appropriate of the additive models for the analysis of the EDB gavage data. This is because it utilizes the full information on both survival times and dosing pattern and makes no assumptions regarding dose rate. Considering the uncertainties involved in risk extrapolation it is apparent that the

Other assumptions are described in the text. Values in the table represent upper 95% confidence limits, except for the proportional hazards model, which the variance estimates were too unstable to derive an upper confidence limit.

^{&#}x27;Assumes 3.0 ppm exposure during time employed.

predictions of this model are fully compatible with the observed mortality in the EDB-exposed cohort.

The proportional hazards model, also sensitive to both the survival times and the variable dosing, gave rather high risks, particularly if one assumes its effect to be on lung cancer, the site of contact for occupational exposure. This was due to the dependence of the model predictions on background rates in humans, when the model parameters were estimated from an animal experiment in which the background rate was zero. It is also rare for an agent that induces lung cancer to affect the background rates, which are primarily due to smoking, in a multiplicative way. Asbestos is a notable exception. (29) On the other hand, at the low exposure estimate (0.9 ppm), assuming EDB's effect is on stomach cancer, the predictions are compatible with the observed cancer deaths at the one plant where measurements were taken (Michigan). Without knowledge of the site of EDB's carcinogenic activity in humans, it is difficult to say whether this model is compatible with the epidemiologic data.

The multistage model with time-to-tumor yields very similar risk estimates as the model that also incorporates the variable dosing pattern, suggesting that the variable dosing was not an important factor in the potency of EDB in the gavage bioassay. With the 3.0 exposure estimate, overall predictions were about three times the observed mortality among the workers. Thus, because the workers' exposure begins comparatively late in life, the additive models which incorporate information on time since exposure begins provide a far better fit to the worker data than those models that do not.

While numerous other models (probit, Weibull, logit, etc.) have been advocated for extrapolation, we have limited our analyses to those with the property of being linear at low doses. Such curves will yield an upper bound for the risk at low doses (30-32) and thus provide a health-protective basis for regulatory decision making.

It should be emphasized that risk assessment makes no claim to providing precise predictions, but rather seeks to generate ball-park estimates. These estimates are intended as plausible upper bounds of risk. Restricting discussion to models used with the gavage data, the one-hit model predicts implausible risks, as does the proportional hazards model using lung cancer deaths, while both the variable dosing and the time-to-tumor forms of the multistage model are compatible with the epidemiologic data. We conclude

that the gavage data are not inherently incompatible with the workers' cancer mortality experience.

The inhalation bioassay was not fraught with the complications of high early mortality and a reduced latency period. This may partially explain why the one-hit model (without an adjustment for latency) applied to the inhalation data predicted cancer risks that were fully compatible with the epidemiologic study. The importance of the latency period is underscored by the fact that most of the tumors observed in the inhalation bioassay were discovered at terminal sacrifice. If we were to exclude such tumors, the predicted excess risks from this bioassay would be halved.

4.2. Route of Exposure

When the doses in the inhalation study were converted to units of mg/kg/day, they were in fact larger than the doses of the gavage study (see Table VI). The time on the study was about double the duration of the gavage bioassay, while the probability of developing tumors was comparable to the probability in the gavage study if one includes the tumors found at terminal sacrifice (104 weeks in the inhalation bioassay). Thus, the gavage study is distinguished from the inhalation study by lower doses,

Table VI. A Comparison of Two Carcinogenicity Bioassays: Gavage and Inhalation

| | Controls | Low dose | High dosc |
|-------------------------------|----------|------------|-----------|
| Gavage | | | |
| Dose" | 0 | 5.37 | 6.66 |
| Response (crude) | 0/20 | 30/50 | 25/49 |
| P (response)b | 0.0 | 0.61 | 0.75 |
| Weeks on study | | | |
| Mean | 53 | 45 | 31 |
| Median | 49 | 47 | 36 |
| Inhalation | | | |
| Dose ^a | 0 | 9.56 | 38.24 |
| Response ^c (crude) | 0/20 | 2/48 24/48 | 39/49 |
| P (response)b | 0.0 | 0.05 0.65 | 0.91 |
| Weeks on study | | | |
| Mean | 103 | 98 | 76 |
| Median | 104 | 104 | 80 |

[&]quot;Doses are in mg/kg/day averaged over the lifetime, converted to human equivalent using surface area as the basis for interspecies scaling

[&]quot;Kaplan-Meier probabilities.

Response rates for low-dose rats in the inhalation study were derived excluding (2/48) and including (24/48) tumors found at terminal sacrifice.

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a higher carcinogenic potency manifested as much shorter latencies, and greater subchronic toxicity.

The high carcinogenic potency in the gavage bioassay was driven largely by the shortened latencies. Adjusting for latency was especially crucial for accurately estimating risks to those whose exposure began late in life. Since even those models incorporating latency period produced larger gavage-based risk estimates than models fitted to the inhalation data, it is possible that extrapolating from the inhalation bioassay underestimates the effects of EDB in humans. That is, humans are potentially as sensitive as the most sensitive site, sex, and species observed in a bioassay using any route. When data from more than one route are available, a risk assessment for human exposure can be based on data from the same route of exposure as that of the humans, if this same route leads to a positive dose-response and other factors are equal (e.g., statistical power of the study, species or strain sensitivity). If, however, bioassay data using a route different from that of the human exposures show a higher potency, these data should not be rejected outright. In the interest of protecting the public health, the bioassay data showing the higher potency should be considered carefully, in conjunction with pharmacokinetic data that may shed light on species and route differences.

4.3. Interspecies Conversion

As demonstrated in Table VI, the mg/unit surface area basis for scaling doses between animals and man yields higher risks for humans than the use of mg/kg body weight. Thus, even the one-hit model would have predicted risks compatible with the workers' mortality, had body weight been used as the scaling factor. In a comprehensive review of the interspecies scaling issue, Davidson et al. (33) conclude that surface area scaling is most likely to provide the correct scaling for carcinogenicity because toxicologic, metabolic, and pharmacokinetic data correlate best when body weight is raised to the power 2/3 or 3/4. With respect to EDB, two lines of argument lead to the conclusion that surface area is likely to be the appropriate basis. (i) EDB acts as a carcinogen at sites apart from point of contact; based on experimental data, at least one pathway involves activation by the cytochrome P-450 mixed function oxidase system. (34) (ii) Contact-site tumors were the most sensitive site for EDB, and the surface area of this target site is proportional to the body surface area.

5. GENERAL IMPLICATIONS

While the relationship between the quantitative aspects of laboratory animal carcinogenesis and human carcinogenesis remains to be delineated, there is evidence that the two may not be far apart for at least some agents. Rowe and Springer (35) showed animal-based estimates of asbestos-induced carcinogenic potency to be within the range of human-based estimates from several studies. Similarly, animal- and human-based estimates derived for the carcinogenic potency of benzene (36) and gasoline (37) were remarkably close. An analysis similar to the one presented here indicated compatibility between a risk assessment for ethylene oxide based on rat mononuclear cell leukemias and leukemias observed in two cohorts of workers involved in the manufacture of ethylene oxide. (38) Crouch and Wilson compared potency estimates based on human data to estimates based on rat and mouse data, and found that in about 2/3 of the comparisons, the estimates differed by less than one order of magnitude. (39) These findings are in direct contradiction to the claims of some scientists (3,4,7,8) that animal-to-human extrapolations have no scientific basis.

In response to reports of a high correlation between rat and mouse carcinogenic potencies, (39-41) Bernstein et al. (42) have shown that rat-mice potency correlations are an artifact of the way doses are determined for the bioassays. Since human doses are not established by experimental protocol, similar potencies for animals and humans are unlikely to be an artifact.

The present paper adds further empirical evidence that quantitative data from animal carcinogenicity studies are a reasonable basis for estimating human cancer risks, and that linear nonthreshold additive models provide a practical means for such risk estimation. This should not be construed to mean that human and animal data will necessarily be consistent. Species differences for some compounds are supported on both theoretical and empirical grounds. When comparing bioassays of the same chemical performed in different species, potencies may differ by more than an order of magnitude. (39-41,43,44) On the other hand, even if the true carcinogenic potencies for two species are close, the estimated potencies may not be. This is because assumptions are required wherever the data are lack-

Well-conducted epidemiologic studies of those occupationally exposed to compounds present at

much lower levels in the environment provide crucial information to environmental health professionals and risk assessors. Even when such studies yield negative results in a hypothesis test, they can serve as a check on the plausibility of animal-based risk estimates. Clearly inappropriate models or assumptions can be discarded, and greater confidence can then be placed in the final risk assessment. Towards this end, occupational studies require more attention to exposure estimation than has generally been the case in the past, and continuing follow-up of exposed cohorts. Twelve years have passed since the closing date of follow-up in the study by Ott et al. (12) While we urge the collection and analysis of such data, we would also emphasize that even in the absence of human data, the continued use of animal data is appropriate.

The field of carcinogenic risk assessment is in its infancy. The primitiveness of methodology echoes the lack of a clear theory of carcinogenesis. However, the gaps in knowledge and the uncertainties in methods do not constitute sufficient justification for abandoning efforts to provide the public with plausible upper bounds for cancer risks due to environmental chemical exposures. For a large number of such exposures, these estimates will necessarily be based on animal data. When quantified human exposure data are available and are related to cancer risk, these data can be useful either as a basis for extrapolation or as a standard for assessing the plausibility of risk estimates based on animal data alone.

6. SUMMARY

Critics of cancer risk projections based on animal bioassays frequently make reference to negative epidemiologic findings, and to reports such as that by Ramsey et al.(2) The analyses presented here demonstrate that low-dose extrapolations using linear nonthreshold additive models are not intrinsically discrepant with epidemiologic observations of cancer mortality.

Additive risk models fitted to data from both gavage and inhalation bioassays predicted risks that were plausible when compared to published data from an epidemiologic study of EDB-exposed workers. However, in rats, EDB is a more potent carcinogen by gavage than by inhalation, with the higher potency manifested in shortened latency periods. Because of the shortened latency period, only models incorporating age at start of exposure were appropriate for the purpose of applying a risk assessment based on the gavage data to workers whose exposure began late in life. Application of a multiplicative model gave implausibly high risk estimates when using lung cancers, though this may have been due to the choice of the wrong target site in humans. Thus, the previously reported overestimate of risk to workers occupationally exposed to EDB was due to a failure to consider their age at start of exposure when extrapolating from an animal bioassay with an exceedingly short latency period.

In the absence of viable alternatives, the results of this investigation support continued use of animal extrapolations to predict human cancer risks from environmental chemicals. Epidemiologic data with quantified exposure estimates can serve as an empirical standard for assessing the plausibility of extrapolation models. Linear nonthreshold additive models have been shown to provide plausible upper bounds when applied with due consideration to the quality of the data from the animal bioassays.

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REFERENCES

- 1. E. L. Anderson and the Carcinogen Assessment Group of the U.S. Environmental Protection Agency, "Quantitative Approaches in Use to Assess Cancer Risk" Risk Analysis 3, 277-295 (1983).
- J. C. Ramsey, C. N. Park, M. G. Ott, and P. J. Gehring, "Carcinogenic Risk Assessment: Ethylene Dibromide," Toxicology and Applied Pharmacology 47, 411-414 (1978).

 3. B. N. Ames, "Cancer and Diet—Reply," Science 224, 668-670,
- 757-760 (1984).
- 4. F. J. Stare, "Controversy About the Risks of EDB (Letter)," New England Journal of Medicine 310, 1387 (1984).
- 5. W. R. Havendar, Editorial, "EDB and the Marigold Option." Regulation, AEI Journal on Government and Society 16, 13 - 17 (1984).
- 6. P. J. Gehring, "The Chemical Industry's Record in Environmental Health," Journal of Environmental Health 47, 58-61 (1984).
- 7. D. A. Freedman and H. Zeisel, "From Mouse to Man: The Quantitative Assessment of Cancer Risks," Technical Report No. 79, Department of Statistics, University of California Berkeley, California (1986).
- 8. B. N. Ames, R. Magaw, and L. S. Gold, "Ranking Possible Carcinogenic Hazards," Science 236, 271-280 (1987).

- 9. National Cancer Institute (NCI), "Bioassay of 1,2-Dibromoethane for Possible Carcinogenicity," NCI Technical
- Report Series No. 86, Bethesda, Maryland (1978). 10. Environmental Protection Agency, "The Carcinogen Assessment Group's Risk Assessment for Ethylene Dibromide (EDB)" (1978).
- 11. Environmental Protection Agency, Office of Pesticide Programs "Ethylene Dibromide" Position Document 4, Washington, D.C. (1983).
- 12. M. G. Ott, H. C. Scharnweber, and R. R. Langner, "Mortality experience of 161 employees exposed to ethylene dibromide in two production units." British Journal of Industrial Medicine 37, 163-168 (1980).
- 13. G. W. Gribble, "Ethylene Dibromide Uproar" (Letter), Chemical and Engineering News 62, 63 (1984).
- 14. National Cancer Institute (NCI), "Carcinogenicity Bioassay of 1,2-Dibromoethane in F344 Rats and B6C3F1 Mice (Inhalation Study)," NCI Technical Report Series No. 210, Research Triangle Park, North Carolina and Bethesda, Maryland (1982).
- 15. D. Krewski, C. Brown, and D. Murdoch, "Determining 'Safe' Levels of Exposure: Safety Factors or Mathematical Models?" Fundamentals of Applied Toxicology 4, \$383-\$394 (1984).
- 16. C. K. Wong, J. M. Winston, C. B. Hong, and H. Plotnick, 'Carcinogenicity and Toxicity of 1,2-Dibromoethane in the Rat," Toxicology and Applied Pharmacology 63, 155-162
- 17. K. S. Crump, "An Improved Procedure for Low-Dose Carcinogenic Risk Assessment from Animal Data," Journal of Environmental Pathology, Toxicology, and Oncology 5, 339-345
- 18. P. Armitage and R. Doll, "The Age Distribution of Cancer and a Multistage Theory of Carcinogenesis," British Journal of
- Cancer 8, 1-12 (1954).

 19. R. Doll, "The Age Distribution of Cancer: Implications for Models of Carcinogenesis," Journal of the Royal Statistical Society 134, 133-166 (1971).
- 20. R. Doll and R. Peto, "Cigarette Smoking and Bronchial Carcinoma: Dose and Time Relationships Among Regular Srnokers and Lifelong Nonsmokers," Journal of Epidemiology and Community Health 32, 303-313 (1978).
- K. S. Crump, "Dose Response Problems in Carcinogenesis," Biometrics 35, 157-167 (1979).
- 22. L. Zeise and E. A. C. Crouch, "Reconciling the Results of Carcinogenesis Bioassays with Benzo(a)pyrene for the Purpose of Risk Assessment," Society for Environmental Toxicology and Chemistry Annual Meeting, Arlington, Virginia (1983).
- T. W. Thorslund, "Estimation of the Effects of Exposure to a Carcinogen that Fluctuates over Time on the Lifetime Risk of Cancer Death," AAAS Pacific Division 63rd Annual Meeting
- 24. K. S. Crump and R. B. Howe, "The Multistage Model with a Tirne-Dependent Dose Pattern: Applications to Carcinogenic Risk Assessment," Risk Analysis 4, 163-176 (1984).
- 25. J. D. Kalbfleisch and R. L. Prentice, The Statistical Analysis of Failure Time Data (Wiley, New York, 1984).
- 26. C. Sawyer, R. Peto, L. Bernstein, and M. C. Pike, "Calculation of Carcinogenic Potency from Long-Term Animal Carcinogensis Experiments," Biometrics 40, 27-40 (1984).
- 27. R. Peto, M. C. Pike, L. Bernstein, L. S. Gold, and B. N. Ames, 'The TD₅₀: A Proposed General Convention for the Numeri-

- cal Description of the Carcinogenic Potency of Chemicals in Chronic-Exposure Animal Experiments," Environmental Health Perspectives 58, 1-12 (1984).
- 28. L. S. Gold, L. Bernstein, J. Kaldor, G. Backman, and D. Hoel, "An Empirical Comparison of Methods Used to Estimate Carcinogenic Potency in Long-Term Animal Bioassays: Lifetable vs. Summary Incidence Data," Fundamentals of Applied Toxicology 6, 263-269 (1986).
- 29. E. C. Hammond, I. J. Selikoff, and H. Seidman, "Asbestos Exposure, Cigarette Smoking and Death Rates," Annals of the New York Academy of Science 330, 473-490 (1979).
- 30. R. Peto, "Carcinogenic Effects of Chronic Exposure to Very Low Levels of Toxic Substances," Environmental Health Perspectives 22, 155-159 (1978).
- 31. K. S. Crump, D. G. Hoel, C. H. Langley, and R. Peto, "Fundamental Carcinogenic Processes and their Implications for Low Dose Risk Assessment," Cancer Research 36, 2973-2979 (1976).
- 32. P. Armitage, "The Assessment of Low-Dose Carcinogenicity," Biometrics Suppl. 38, 119-129 (1982).
- 33. I. W. F. Davidson, J. C. Parker, and R. P. Beliles, "Biological Basis for Extrapolation Across Mammalian Species," Regul Toxicol Pharmacology 6, 211-237 (1986).
- 34. P. J. van Bladeren, J. J. Hoogeterp, D. D. Breimer, and A. van der Glen, "The Influence of Disulfiram and Other Inhibitors of Oxidative Metabolism on the Formation of 2-Hydroxyethyl-mercapturic Acid from 1,2-Dibromoethane by the Rat," Biochemical Pharmacology 30, 2983-2987 (1981).
- 35. J. N. Rowe and J. A. Springer, "Asbestos Lung Cancer Risks: Comparison of Animal and Human Extrapolations," Risk Analysis 6, 171-180 (1988).
- 36. California Department of Health Services, "Health Effects of Benzene, Report to the Scientific Review Panel, Part
- 37. P. E. Enterline, "A Method for Estimating Lifetime Cancer Risks from Limited Epidemiologic Data," Risk Analysis 7, 91-96 (1987).
- 38. I. Hertz-Picciotto, R. R. Neutra, and J. F. Collins, "Carcinogenicity of Ethylene Oxide: A Comparison of Dose-Response Data in Animals and Humans" (letter), Journal of the American Medical Association 257, 2290 (1987).
- E. Crouch and R. Wilson, "Interspecies Comparison of Carcinogenic Potency," Journal of Toxicology and Environmental Health 5, 1095-1118 (1979).
- 40. E. A. C. Crouch, "Uncertainties in Interspecies Extrapolations of Carcinogenicity," Environmental Health Perspecives 50, 321-327 (1983).
- 41. D. W. Gaylor and J. J. Chen, "Relative Potency of Chemical Carcinogens in Rodents," Risk Analysis 6, 283-290 (1986).
- 42. L. Bernstein, L. S. Gold, B. N. Ames, M. C. Pike, and D. G. Hoel, "Some Tautologous Aspects of the Comparison of Carcinogenic Potency in Rats and Mice," Fundamentals of Applied Toxicology 5, 79-86 (1985).
- 43. D. M. Siegel, I. Hertz-Picciotto, M. Lipsett, and R. Neutra, "Health Effects of Cadmium. Part B, Report to the Air Resources Board." California Department of Health Services (1986).
- 44. I. Hertz-Picciotto, "The Role of Assumptions in Quantitative Cancer Risk Estimation," American Public Health Association 114th Annual Meeting (1986).

Principles of Health and Safety in Agriculture. Ed. by J.A. Dosman and D.W. Cockcroft. Boca Raton, CRC Press. 1989. pp. 39-44.

Use of Biological Assays in Short--Term Assessment of Inhaled Substances

Joseph D. Brain

INTRODUCTION

Workers in the agricultural industry are exposed to an exceptionally wide variety of inhaled particles. These include fertilizers, pesticides, and herbicides as well as resuspended soil. Moreover, the composition of the soil (for example, the fraction which is free silica) varies from place to place. Other workers are exposed to complex grain dusts, such as that coming from various cereal grains (wheat, barley, rye, oats, com), as well as various contaminants such as insects, mites, rodent debris, and fungi. This wide array of complex dusts presents problems in assessing the potential risk of various occupational exposures in agriculture.

In order to understand such exposures, it is possible to measure responses at the molecular, cell, organ, or organismic level. All approaches reflect the need to evaluate the toxicology of materials to which agricultural workers are exposed so that we can take appropriate preventive action. Government, unions, and industry now face the difficult task of assessing the toxicology of a wide variety of new chemicals and especially complex mixtures. The creativity of chemists who synthesize new compounds, the availability of new technologies, and finally the competitiveness of agriculture ensure that there will be a continuing stream of new aerosol exposures whose potential for damage must be assessed. Since they are new, epidemiology fails to provide information about health effects. Nevertheless, a guide to potential toxicity is needed to help design both appropriate control strategies and medical surveillance studies for humans employed in agriculture.

How can the risk of human pulmonary disease caused by exposure to complex and often poorly characterized dusts in the agricultural industry be predicted? Risk assessment may include: (1) air monitoring and physical and chemical characterization of collected dusts; (2) epidemiologic studies of humans; (3) controlled experimental exposures of humans in the laboratory; (4) chronic lifetime animal studies; (5) short-term animal bloassays; and (6) in vitro tests of mammalian cells. This paper emphasizes the fifth method of analysis and discusses the use of short-term animal bloassay systems to determine the health effects of inhaled particulates.

Animal studies have numerous advantages since ethical problems are minimized. The possibility of more serious disease can be assessed, and there are few limits to the invasiveness of the diagnostic procedures used. For example, long-term inhalation exposures of animals, followed by functional or histopathological studies of their lungs, have been used to study asbestos, 1 crystalline silica, 2 and coal dust. 3 A problem is that such studies are costly and time consuming. A

typical lifetime study in rodents costs between 0.5 and 3 million dollars and may take 3 to 5 years to plan and complete. It is also difficult to obtain quantitative estimates of toxicity using standard pathological analyses. Morphometric measures based on extensive sampling of lung tissue as well as physiological or biochemical assessment may be required.

Clearly, there is a need for short-term tests. If large numbers of materials are to be analyzed, it is essential to have assays that are relatively inexpensive and that yield results in weeks or months, not years. Many investigators have promoted the use of in vitro assays to assess the potential toxicity of inhaled aerosols.4-7 In vitro systems have advantages of reproducibility, cost, and specificity. Several tissue culture systems have been developed. 8.9 However, because the human pulmonary response to inhaled particles is the result of complex interactions involving many different cell types within the lung, the results obtained may be spurious. For example, inflammation involves recruitment of neutrophils, platelets. and serum proteins to the injured lung. Fibrogenesis involves the action of fibrogenesis-stimulating factors secreted by one cell (e.g., a macrophage) on another cell (a fibroblast). These essential interactions are rarely reproduced in any in vitro

Short-term in vivo assays can be considered as an alternative to short-term in vitro tests, because the short-term response of small animals to dusts is sufficiently similar to the human response to have predictive values when properly calibrated and interpreted. The major mechanisms of lung injury¹⁰ are common to most mammals.

THE HAMSTER BIOASSAY

The hamster bioassay features the use of bronchoalveolar lavage (BAL). During the last decade, BAL has been used increasingly to assess lung injury in animals and man. BAL has been employed to discriminate among toxic agents such as metal salts or mineral dusts. 11.12 Key issues in the application of BAL to inhalation toxicology are the specificity and sensitivity of the procedure. What is the smallest amount of dust which causes a measurable response? More important, what is the ability of BAL to discriminate among dusts of varying toxicities and those producing different resulting lesions? To what extent does BAL have predictive value? Can one examine acute events and describe long-term irreversible chronic changes?

We have developed a short-term (1 to 30 d postexposure) animal bioassay system in which the toxicity of a particular dust may be estimated by comparison to known dusts with a

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demonstrated range of toxicities for human pulmonary disease. We employ hamsters exposed to dusts by either inhalation or by intratracheal instillation and quantify the response by measuring biochemical and cellular indicators in BAL fluid. The parameters measured represent a wide spectrum of possible responses to inhaled particles, including inflammation, pulmonary edema, cellular damage, cellular secretion, and endocytic capacity of pulmonary macrophages. We have calibrated the system with dusts for which there is considerable human experience. Cellular and biochemical changes were measured in BAL of hamsters after exposure to α -quartz, iron oxide, and aluminum oxide. $^{12}\alpha$ —Quartz is a highly toxic, fibrogenic mineral dust, whereas aluminum oxide and iron oxide are both of low toxicity.

One day after exposure, the levels of β -N-acetylglucosaminidase were significantly elevated by exposure to the 0.75- and 3.75-mg doses of all three dusts (see Figure 1). However, the response to α -quartz was greater than the response to the other two dusts, especially at the highest dose. β -N-acetylglocosaminidase is an example of a lysosomal enzyme that is released from cells during phagocytosis, cell injury, or cell death. Polymorphonuclear neutrophils (PMNs), macrophages, and type II cells all contain acid hydrolases. Excessive release of lysosomal enzymes may elicit unwanted proteolysis from cathepsins or membrane destruction by phospholipases.

 α -Quartz also elevated albumin levels in lavage fluid at both 0.75- and 3.75-mg doses as shown in Figure 2. The highest dose caused a more than 40-fold increase above control levels. Aluminum oxide and iron oxide were also associated with an increase at 3.75 mg, but albumin levels clearly distinguished between these relatively nontoxic dusts and the highly fibrogenic α -quartz. Albumin is primarily a

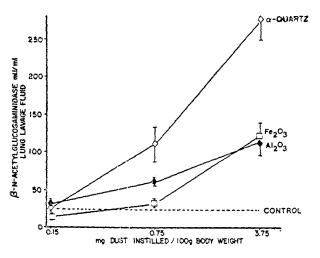


FIGURE 1. Dose-response curve for β -N-acetylglucosaminidase 1 d after instillation of particles. p < 0.01 for all points except 0.75 mg iron oxide and 0.15 mg aluminum oxide (p < 0.05), and 0.15 mg α -quartz (not significant). Values are mean \pm standard errors. (Adapted from Beck, B. D., Brain, J. D., and Bohannon, D. E., Exp. Lung Res., 2, 289, 1981. With permission.)

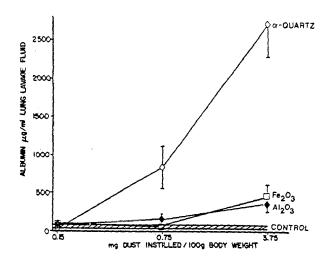


FIGURE 2. Dose-response curve for albumin in extracellular supermatant of lung lavage fluid 1 d after exposure to iron oxide, aluminum oxide, or α -quartz. The Wilcoxon rank-sum test was used to compare experimentals and saline-only controls. p <0.01 for all points except 0.75 mg aluminum oxide and all 0.15-mg samples (not significant). Values represent mean \pm standard errors. (Adapted from Beck, B. D., Brain, J. D., and Bohannon, D. E., Exp. Lung. Res., 2, 289, 1981. With permission.)

serum protein whose presence in BAL is due to passage across damaged endothelial and epithelial barriers. Albumin is usually the most abundant protein in BAL. ^{16,17} Elevated albumin levels indicate pulmonary edema, a common manifestation of acute pulmonary injury. ^{12,18}

Figure 3 illutratres that α -quartz also causes depressed macrophage function. The lambda values shown are the fraction of radioactive gold colloid which was ingested 90 min after it had been instilled through the trachea. Brain and Corkery¹⁹ provide details of this assay which estimate the endocytic activity of macrophages in situ. At a dose of 3.75 mg of α -quartz, less than 30% of the gold was ingested; iron oxide and aluminum oxide have no significant effect on lambda.

The full bioassay includes a number of other parameters such as peroxidase, elastase; hemoglobin, as well as the numbers of erythrocytes, neutrophils, and macrophages. An essential aspect of bioassays like this is to compare the responses of unknown dusts with other well-characterized standards. Both positive and negative controls should be used. The best calibrating materials would be those for which there is a considerable experience in humans such as the dusts shown in Figures 1 to 3. Then the type and intensity of response for a new unknown dust could be compared to these standards.

A key feature of assays utilizing lung lavage is the time course of the response. Some agents will yield similar responses when examined soon after exposure. However, the more toxic material may frequently exhibit a more persistent change in the cellular and enzymatic parameters than nontoxic controls. For example, there was a prolonged elevation in the numbers of macrophages and PMNs with quartz, but not with iron oxide. PMN numbers in the lung lavage fluid were

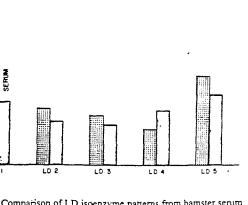


FIGURE 4. Comparison of LD isoenzyme patterns from hamster serum and from lung lavage fluid of hamsters exposed to 100% O₂ for 96 h. (Adapted from Beck, B. D., Gerson, B., Feldman, H. A., and Brain, J. D., Toxicol. Appl. Pharmacol., 71, 59, 1983. With permission.)

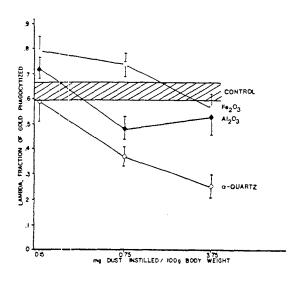


FIGURE 3. Dose-response curve for lambda assay 1 d after exposure to iron oxide, aluminum oxide, or α -quartz. The Wilcoxon rank-sum test was used to compare experimentals and saline only controls. p <0.01 for 0.75 and 3.75 mg α -quartz, 0.75 mg aluminum oxide; p <0.05 for 0.15 mg iron oxide. Values represent mean \pm standard errors. (Adapted from Beck, B. D., Brain, J. D., and Bohannon, D. E., Exp. Lung. Res., 2, 289, 1981. With permission.)

highest 4 d after exposure to α -quartz, although after 2 weeks they still had not approached control levels.¹²

A somewhat different pattern was observed for lactate dehydrogenase (LDH) in lavage fluid. This is a cytoplasmic enzyme involved in energy metabolism; its extracellular release is associated with cell injury or death. LDH levels in lung lavage fluid were highest 1 d after exposure to both iron oxide and α -quartz. In time, LDH levels declined significantly in the quartz-exposed animals and only slightly in the iron oxide-exposed animals. Nevertheless, the levels in the quartz animals remained higher than those in the iron oxide-exposed animals at all times. These effects were observed at relatively low levels of quartz compared to levels used in animal models of chronic silicosis.

Application of this system to dusts produced by the eruption of Mt. St. Helens volcanic ash suggested that volcanic ash has low to moderate toxicity.20 We concluded that adverse health effects in human populations are unlikely except with high or prolonged exposure. Surfactant levels in BAL in rats after quartz and Mt. St. Helens volcanic ash exposure have been studied by Martin and co-workers.21 Quartz causes a prolonged elevation in PMN numbers and surfactant levels. The effects were much less marked with volcanic ash than with quartz. These observations are consistent with histopathological studies of lungs of exposed animals which demonstrated much greater fibrogenicity of α -quartz than of volcanic ash. These studies show the usefulness of BAL in providing a rapid evaluation of the toxicity of poorly characterized samples. Useful results can be obtained even when chemical analyses of epidemiological studies are not available for toxicity estimates.

THE LA MARINE

IDENTIFYING SOURCES OF DAMAGE INDICATORS: LDH ISOENZYMES

We are searching for other ways of making the assay more interpretable. As discussed earlier, LDH is released from cells in response to toxic particles. However, if LDH is recovered in the cell-free supernatant of lung lavage fluid, where does it come from? Is the source inflammatory cells (macrophages or PMNs), serum, epithelial cells, or endothelial cells? Beck et al.²² have used isoenzyme analysis to infer the sources of LDH.

To differentiate among types of injury, we monitored changes in LDH isoenzyme patterns in BAL after a range of injuries: α-quartz, hyperoxia, the detergent Triton X-100, and SO₂. The LDH isoenzyme patterns in BAL were evaluated and compared with patterns from hamster lung homogenates, red blood cells, macrophages, PMNs, type II cells, and serum. The isoenzyme pattern in BAL from quartz-exposed animals resembled that of the PMNs and macrophages, suggesting phagocytic cell death. In contrast, BAL from Triton X-100-treated animals had an isoenzyme pattern similar to that of the lung homogenate and red blood cells. Exposure to 100% O₂ for 4 d produced an isoenzyme pattern similar to serum, an observation consistent with the demonstrated effects of O₂ on the capillary endothelium.

Figure 4 presents graphically the percentage of each LD isoenzyme from serum or from lung lavage fluid of Syrian golden hamsters exposed to 100% O₂ for 96 h. The distribution of the five LD isoenzymes is similar and consistent with the hypothesis that oxygen toxicity caused damage to the airblood barrier. Serum LD and other serum proteins leaked into alveolar spaces and were subsequently recovered by lavage.

In Figure 5 the LD pattern is shown for: (1) supernatant from BAL recovered from hamsters exposed to iron oxide aerosol and (2) hamster peritoneal PMNs. The LD patterns shown in Figure 5 are markedly different from those seen in Figure 4. For example, there is little LD1 (<3%), but a great deal of LD5 (-60%). The similarity in pattern suggests that the

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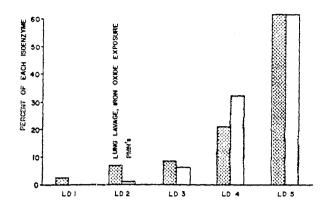


FIGURE 5. Comparison of LD isoenzyme patterns from hamster peritoneal PMNs and from lung lavage fluid of hamsters exposed to 3.75 mg iron oxide per 100 g body weight. (Adapted from Beck, B. D., Gerson, B., Feldman, H. A., and Brain, J. D., Toxicol, Appl. Pharmacol., 71, 59, 1983. With permission.)

LD could be coming from PMNs. Macrophages have a similar LD composition, so they also may be a source.

AUTOMOBILE WASTE OIL COMBUSTION PRODUCTS

This assay is particularly suited for analyzing new complex agents which are just being introduced into the environment. We have recently investigated the pulmonary toxicity of respirable particulates from an air-atomizing oil space heater using automobile waste crankcase oil (AWO).²³ A combustion sample was prepared from AWO from a service station by Dr. R. E. Hall of the U. S. Environmental Protection Agency, using an air-atomizing oil burner rated at 250,000 BTU/h heat input. Respirable particulates were collected from a dilution tunnel by electrostatic precipitation using a massive air volume sampler.²⁴ Analysis of the particles showed certain metals were present at relatively high levels, for example: Pb, 75.6 mg/g; Zn, 23.0 mg/g; and Fe, 5.3 mg/g.

At 1 d postexposure, there was extensive pulmonary injury as demonstrated by cellular and biochemical indicators in BAL: (1) elevated levels of albumin, (2) increased extracellular glucosaminidase, and (3) impaired pulmonary macrophage phagocytosis. The injury was often greater than that seen in response to toxic α -quartz. Some of the data obtained are shown in Figures 6 to 8.

However, assays of BAL up to 14 d post-AWO exposure demonstrated that most indicators rapidly approached control values. This is in contrast to the persistent inflammation caused by α -quartz. As shown in Figure 9, LDH values approached control values at 2 weeks after intratracheal instillation of AWO. Following quartz exposure, the LDH level remains elevated. This suggests that the toxic effects of AWO stem from soluble components which are rapidly cleared. AWO may be less likely to cause chronic pulmonary disease than α -quartz unless exposure persists. Acute injury as manifested by bronchitis or increased susceptibility to infection may be a more likely outcome than fibrosis.

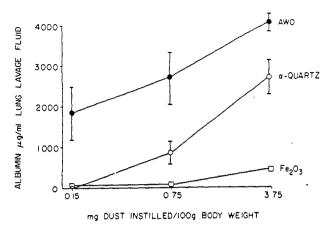


FIGURE 6. Concentration of albumin in the cell-free supernatant of BAL fluid. The effects of iron oxide, α-quartz, and combustion products of AWO are shown 1 d after intratracheal instillation. Values are mean ± standard errors. (Adapted from Beck, B. D., Brain, J. D., and Wolfthal, S. F., Inhaled Particles IV, Dodgson, J., Ed., British Occupational Hygiene Society,

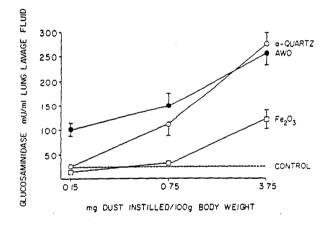


FIGURE 7. Concentration of β -N-glucosaminidase in the cell-free supernatant of lavage fluid after exposure to iron oxide, α -quartz, and AWO. Values are mean \pm standard errors. (Adapted from Beck, B. D., Brain, J. D., and Wolfthal, S. F., *Inhaled Particles IV*, Dodgson, J., Ed., British Occupational Hygiene Society, Edinburgh, Scotland.)

By comparing the response to AWO with the response to the same doses of toxic α -quartz and nontoxic iron oxide, we conclude that the AWO combustion products have a high potential to cause acute lung injury. Both soluble and insoluable components of AWO can produce lung injury. Some, but not all, of these effects are due to acidity and divalent cations, such as lead, which are present at high levels.

CONCLUSION

Edinburgh, Scotland.)

Experimental pathology has frequently advanced because of the addition of new diagnostic tools. During the last decade, BAL has emerged as a very useful tool in the assessment of lung injury. It is applicable to both animal models exposed to inhaled particles and gases in a laboratory and to humans

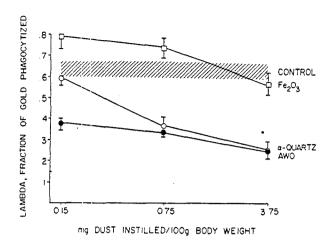


FIGURE 8. The fraction of gold particles, lambda ingested by macrophages in situ, is shown. Measurements were made 1 d after exposure to iron oxide. α-quartz, and AWO. Values are mean ± standard errors. (Adapted from Beck, B. D., Brain, J. D., and Wolfthal, S. F., Inhaled Particles IV, Dodgson, J., Ed., British Occupational Hygiene Society, Edinburgh, Scotland.)

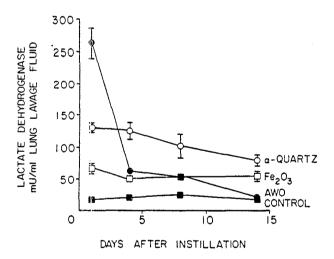


FIGURE 9. Time course for LDH in the extracellular supernatant fraction of lung lavage fluid after exposure to 3.75 mg iron oxide, α -quartz, or AWO per 100 g body weight. Values are mean \pm standard errors. (Adapted from Beck, B. D., Brain, J. D., and Wolfthal, S. F., Inhaled Particles IV. Dodgson, J., Ed., British Occupational Hygiene Society, Edinburgh, Scotland.)

encountering exposures to the same agents in occupational and urban environments. Information can be gathered from BAL relating to the extent and type of lung injury and the mechanisms involved. Needed are more extensive comparisons of injury as judged by other approaches with the results of BAL. For example, short-term bioassay results can be integrated with industrial hygiene and epidemiology results as was done in a recent study of talc and granite dusts.²⁵ It is also likely that other constituents of BAL can be quantified which will help make bioassays utilizing BAL more specific and

sensitive. The use of BAL in short-term animal assays can be an important source of information regarding the toxicity of new and poorly characterized inhaled particles.

REFERENCES

- Brody, A.R. and DeNee, P.B., Biological activity of inorganic particles in the lung, CRC Crit. Rev. Toxicol., 7, 277, 1981.
- Gross, P., DeVilliers, A.J., and deTrevelle, R.T.P., Experimental silicosis, Arch. Pathol., 84, 87, 1967.
- Busch, R.H., Filipy, R.E., Karagianes, M.T., and Palmer, R.F., Pathologic changes associated with experimenal exposure of rats to coal dust, *Environ. Res.*, 24, 53, 1981.
- Dean, J.H., Boorman, G.A., Luster, M.I., Adkins, B., Jr., Lauer, L.D., and Adams, D.O., Effect of agents of environmental concern on macrophage functions, in *Mononuclear Phagocyte Biology*. Volkman, A., Ed., Marcel Dekker, New York, 1984, 473.
- Liu, W.K., Tsao, S.W., and Wong, J.W.C., In vitro effects of fly ash on alveolar macrophages, Conservation Recycling, 7, 361, 1984.
- Snella, M.-C., Manganese dioxide induces alveolar macrophage chemotaxis for neturophils in vitro, *Toxicology*, 34, 153, 1985.
- Hatch, G.E., Boykin, E., Graham, J.A., Kewtas, J., Pott, F., Loud, K., and Mumford, J.L., Inhalable particles and pulmonary host defense: in vivo and in vitro effects of ambient air and combustion particles, Environ. Res., 36, 67, 1985.
- Kaw, J.L., Tissue culture in pneumoconiosis. CRC Crit. Rev. Toxicol., 5, 103, 1977.
- Miller, K., The effects of asbestos on macrophages, CRC Crit. Rev. Toxicol., 5, 319, 1978.
- Fantone, J.C. and Ward, P.A., Mechanisms of lung parenchymal injury, Am. Rev. Respir. Dis., 130, 484, 1984.
- Henderson, R.F., Rebar, A.H., Pickrell, J.A., and Neulton, G.J., Early damage indicators in the lung. III. Biochemical and cytological response of the lung to inhaled metal salts. *Toxicol. Appl. Pharma*col., 51, 123, 1979.
- Beck, B.D., Brain, J.D., and Bohannon, D.E., An in vivo hamster bioassay to assess the toxicity of particulates for the lungs, *Toxicol. Appl. Pharmacol.*, 66, 9, 1982.
- Brain, J.D., Knudson, D.E., Sorokin, S.P., and Davis, M.A., Pulmonary distribution of particles given by intratracheal instillation or by aerosol inhalation. *Environ. Res.*, 11, 13, 1976.
- Weissman, G., Smolin, J.E., and Korchak, H.M., Release of inflammatory mediators from stimulated neutrophils, N. Engl. J. Med., 303, 27, 1980.
- Hook, G.E.R., Extracellular hydrolases of the lung. *Biochemistry*, 17, 520, 1978.
- Bell, D.Y., Haseman, J.A., Spock, A., McLennan, G., and Hook, G.E.R., Plasma proteins of the bronchoalveolar surface of the lungs of smokers and nonsmokers, Am. Rev. Respir. Dis., 124, 72, 1981.
- Merrill, W., O'Hearn, E., Rankin, J., Naegel, G., Matthay, R.A., and Reynolds, H.Y., Kinetic analysis of respiratory tract proteins recovered during a sequential lavage protocol, Am. Rev. Respir. Dis., 126, 617, 1982.
- Chichester, C.O., Palmer, K.C., Hayes, J.A., and Kagen, H.M., Lung lysyl oxidase and prolyl hydroxylase: increases induced by cadmium chloride inhalation and the effect of beta-aminopropionitrile in rats, Am. Rev. Respir. Dis., 124, 709, 1981.
- Brain, J.D. and Corkery, G.C., The effect of increased particles on the endocytosis of radiocolloids by pulmonary macrophages in vitro: competitive and cytotoxic effects, in *Inhaled Particles IV*, Walton, W.H., Ed., Perfamon, New York, 1977, 551.
- Beck, B.D., Brain, J.D., and Bohannon, D.E., The pulmonary toxicity of an ash sample from Mt. St. Helens volcano, Exp. Lung Res., 2, 289, 1981.
- Martin, T.R., Chi, E.Y., Covert, D.S., Hodson, W.A., Kessler, D.E., Moore, W.E., Altman, L.C., and Butler, J., Comparative effects of inhaled volcanic ash and quartz in rats, Am. Rev. Respir.

- Dis., 128, 144, 1983.
- Beck, B.D., Gerson, B., Feldman, H.A., and Brain, J.D., Lactic dehydrogenase isoenzymes in hamster lung lavage fluid after lung injury, Toxicol. Appl. Pharmacol., 71, 59, 1983.
- Beck, B.D., Brain, J.D., and Wolfthal, S.F., Assessment of lung injury produced by particulate emissions of space heaters burning automobile waste oil, in *Inhaled Particles VI*, Dodgson, J., Ed., British Occupational Hygiene Society, Edinburgh, Scotland, in
- press.
- Hall, R.E., Crooke, M.W., and Barbour, R.L., Comparison of air pollutant emissions from vaporizing and air atomizing waste oil heaters, J. Air Pollut, Control Assoc., 33, 683, 1983.
- Beck, B.D., Feldman, H.A., Brain, J.D., Smith, T.J., Hallock, M., and Gerson, B., The pulmonary toxicity of talc and granite dust as estimated from an in vivo hamster bioassay, Toxicol. Appl. Pharmacol., 87, 222, 1987.

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ARE YOUR MUSHROOMS SAFE TO EAT?

Raw commercial mushrooms, obtained from the supplier of local food stores, have been tested in a bioassay (Toth and Erickson, 1986) similar to those used for synthetic organic chemicals. We can therefore perform a risk assessment on raw mushrooms similar in all respects to the risk assessments performed on synthetic organic chemicals. In the mushroom experiment, there was one control group of 50 mice for each sex and one experimental group of 50 mice for each sex, the former kept on a normal diet and the latter fed the material under test at an average rate of about 157,000 mg/kg-day for their lifetime (assuming mice weigh 30 g). Feeding of the dosed group was ad lib mushrooms (without other feed) 3 days/week, normal diet 4 days/week; while the control group received the normal diet. Average mushroom consumption was 11 g/day/mouse during days on which mushrooms were the only food available (mushrooms are about 90% water).

The experiment was continued for the natural lifetime of the animals, and no differences were seen in the lifetime of the dosed animals versus the control groups. However, the average weight of the dosed animals was substantially lower than the average weight of the control groups. There were increased incidences of tumors in several organs:

| Tumor site:type | Sex | Control Group | Dosed Group | Significance |
|---------------------|-----|---------------|-------------|----------------------|
| Bone:various | F | 0/50 | 8/50 | 0.003 |
| Bone:various | М | 0/50 | 8/50 | 0.003 |
| Forestomach:various | F | 0/50 | 19/50 | 2.3×10^{-7} |
| Forestomach:various | М | 2/50 | 14/50 | 0.00094 |
| Liver:hepatoma | F | 0/50 | 4/50 | 0.059 |
| Liver:hepatoma | М | 1/50 | 6/50 | 0.055 |
| Lung:All tumors | F | 13/50 | 20/50 | 0.1 |
| Lung:Adenoma | F | 6/50 | 12/50 | 0.096 |
| Lung:Adenocarcinoma | F | 7/50 | 11/50 | 0.22 |
| Lung:All tumors | М | 17/50 | 31/50 | 0.0045 |
| Lung:Adenoma | М | 12/50 | 24/50 | 0.006 |
| Lung:Adenocarcinoma | М | 9/50 | 13/50 | 0.23 |

From these results we can construct the following estimates for potency (q, and q,*) in mice.

| Tumor site:type | Sex | q ₁ (kg-d/mg) | q ₁ * (kg-d/mg) |
|---------------------|-----|--------------------------|----------------------------|
| Bone:Various | F | 1.1 × 10 ⁻⁶ | 1.9 × 10 ⁻⁶ |
| Elone:Various | М | 1.1 × 10 ⁻⁶ | 1.9 × 10 ⁻⁶ |
| Forestomach:Various | щ | 3.0×10^{-6} | 4.4 × 10 ⁻⁶ |
| Forestomach:Various | М | 1.8 × 10 ⁻⁶ | 2.9 × 10 ⁻⁶ |
| Lung:Total | F | 1.3 × 10 ⁻⁶ | 2.9 × 10 ⁻⁶ |
| Lung:Total | М | 3.5 × 10 ⁻⁶ | 5.8 × 10 ⁻⁶ |

Using the EPA methodology, the value chosen from these would be the highest value of q_1^* that corresponds to a statistically significant result — 5.8×10^{-6} kg-d/mg — and this value would then have to be extrapolated to humans using a surface area factor of (70 kg/30 g)^{1/3} = 13.26. Such an approach leads to an upper bound estimate of carcinogenic potency in humans of 7.7×10^{-5} kg-d/mg.

What does this imply for eating raw mushrooms in your salad?

- (1) A upper bound estimate of potency of 7.7×10^{-5} kg-d/mg implies that the dose rate required to give an upper bound estimate of risk of 10^{-6} is 0.013 mg/kg-d, or about 23 g (0.82 oz) per lifetime.
- (2) A consumption of 1 oz/month (13.3 mg/kg-d) of raw mushrooms corresponds to an upper bound estimate of lifetime risk of 1×10^{-3} .
- (3) According to Toth and Erickson (1986), estimated annual US consumption of these mushrooms was 340×10^6 kg in 1984-1985. This was an annual average per capita consumption of about 55 mg/kg-d, corresponding to an upper bound estimate of lifetime risk of 4.3×10^{-3} . Presumably not all the mushrooms would be eaten raw, but we have no idea what would be the effect on the carcinogenicity of the mushrooms of cooking them.
- (4) With the figures given in (3), the upper bound estimate of the annual number of cancers expected in the US to be due to mushrooms is about 8500!

Comment

Mushrooms are known to contain various compounds, including hydrazine analogs, that are mutageriic *in vitro* and/or carcinogenic in laboratory animals under certain conditions. An extract of mushrooms of the type tested has also been shown to be mutagenic. However, the spectrum of tumors found in this experiment on raw mushrooms was not what might be expected from the known carcinogenic compounds present in the mushrooms. Presumably there are different carcinogenic compounds are also present, or there was an interaction with other chemicals present.

References

Toth, B. and J. Erickson. 1986. Cancer Induction in mice by feeding of the uncooked cultivated mushroom of commerce *Agaricus Bisporus*. Cancer Research 46 (1986) 4007–4011.

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The Rat as an Experimental Animal

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The development and characterization of many inbred, congenic, and recombinant strains of rats in recent years has led to the detailed genetic description of this species, especially in regard to its major histocompatibility complex. This information has contributed substantially to the study of comparative genetics and has greatly enhanced the utility of the rat in a variety of areas of biomedical research. This article focuses on the use of the rat in immunogenetics, transplantation, cancer-risk assessment, cardiovascular diseases, and behavior.

THE RAT IS A MAJOR EXPERIMENTAL ANIMAL IN TRANSPLANtation, immunology, genetics, cancer research, pharmacology, physiology, neurosciences, and aging. The strains and randomly bred stocks that have been used almost exclusively are derived from the Norway rat (Rattus norvegicus), which is thought to have originated in the area between the Caspian Sea and Tobolsk, extending as far east as Lake Baikal in Siberia. It spread to Europe and the United States with the development of commerce in the 18th century, and by the middle of the 19th century it was being used extensively for studies in anatomy, physiology, and nutrition. The first inbred lines were developed at the beginning of the 20th

century by H. H. Donaldson, W. E. Castle, and their colleagues for studies in basic genetics and in cancer research (1). Further development and genetic characterization of inbred, congenic, and recombinant strains occurred in the United States, Japan, and Czechoslovakia (2), and several reviews have documented these developments in detail (3-5). In addition to its experimental uses, the rat has a worldwide economic and medical impact, since it destroys one-fifth of the world's crops each year, carries many diseases that are pathogenic for humans, and kills many children by direct attack

This review will focus on current work utilizing the rat in immunogenetics, transplantation, cancer-risk assessment, cardiovascular diseases, and behavior. In these areas of research, the rat has the advantage of being a well-characterized, intermediate-sized rodent without the disadvantages, both scientific and economic, of larger animals and without many of the technical disadvantages of smaller rodents.

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Immunogenetics

Considerable effort has been expended in recent years to develop and characterize inbred, congenic, and recombinant strains of rats, and a wide variety of these genetic resources is now available (3, 4, 7–9). Several compilations of basic data have been assembled (5), and current developments are regularly updated in the Workshops on Alloantigenic Systems of the Rat (10) and in the Rat Newsletter (11). This work has also provided insight into the comparative genetics of the major histocompatibility complex (MHC) and of MHC-linked genes affecting growth and development. The level of polymorphism of MHC antigens in the rat is very low compared to that of other species; the class I antigens have been most extensively studied. Nonetheless, the resistance to disease, reproductive capacity, and ecological stability of the rat do not differ from those of other species. Hence, the biological significance of MHC polymorphism remains a mystery.

The structure of the MHC in the rat (RT1) based on data from serological, molecular, and functional studies is shown in Fig. 1 (3, 12, 13). The general organization of the class I and class II loci is the same as in the mouse but different from that in all other species studied: the class II loci are interspersed between class I loci rather than following them sequentially (14). This observation indicates that (i) the rat and the mouse formed separate genuses after the divergence of the prototypic Muridae, (ii) the evolutionary conservation of the MHC persists despite internal rearrangements, and (iii) the function of these loci does not depend, at least to a first approximation, on their specific order or on their polymorphism.

The RT1.A and RT1.E loci encode classical class I transplantation antigens and appear to be the homologs of the mouse H-2K and H-2K2D loci. There are several other class I loci in the vicinity of RT1.A, and the best defined are the diallelic RT1.F and Pa (pregnancyassociated) loci (3, 13, 16). The antigen encoded by the Pa locus was first identified on the surface of the basal trophoblast in the allogeneic WF(u) × DA(a) mating by alloantisera and by monoclonal antibodies made by the WF mother (17). This antigen carries an epitope that is broadly shared among other class I antigens, but does not have the allele-specific epitope of a classical class I transplantation antigen. Immunohistochemical and electron microscopic studies (18) showed that both the Pa and Aa antigens are also on most somatic tissues and that they are carried by separate molecules. The mapping of the A, F, and Pa loci is based on the use of various combinations of inbred, congenic, and recombinant strains; a number of monoclonal antibodies; and specifically designed alloantisera. No recombinants among these loci have yet been found, but immunoprecipitation and peptide mapping studies have demonstrated that they are separate molecules: hence, the order of these loci in Fig. 1 must be considered tentative. The RT1.G and RT1.C loci encode class I antigens that appear to be homologous to the mouse Qa/TL antigens, but these loci have not yet been well characterized (19).

The class II loci RT1.B and RT1.D were detected serologically and by molecular analysis (3), whereas RT1.H has been detected only by molecular analysis (12). The B and D loci appear to be homologous to the mouse A and E loci, and the H locus appears to be homologous, in part, to the mouse $\psi A\beta 3$ pseudogene and the human HLA-DP locus.

The growth and reproduction complex (grc) is closely linked to the MHC (20). In the homozygous state, it is semilethal in males and females, causes small body weight in both males and females (dw-3), and causes male sterility and reduced female fertility (ft). These defects are similar to some of those associated with the t haplotypes in the mouse, but the grc is not homologous to the t genes since it does not cause segregation distortion or suppression

of recombination (3, 20). The fertility defect occurs at the same stage of gametogenesis in both males and females: there is complete arrest of spermatogenesis at the primary spermatocyte stage, and a partial defect in the maturation of the primary ovarian follicle. The grc acts at an early stage of meiotic prophase I; it is not associated with any known chromosomal or hormonal abnormality; and it increases susceptibility to chemical carcinogens in both males and females (21). Its effects are probably due to the deletion of a segment of the chromosome close to the MHC (22). If so, then the increased susceptibility to cancer may be due to the loss of cancer suppressor genes, or anti-oncogenes, as in retinoblastoma and Wilms' tumor in humans (23). Hence, these animals may provide a unique system in which to study the genetics of susceptibility to cancer.

The homozygous grt genotype (20 to 25% in utero mortality) can interact with the heterozygous Tal/+ gene, which is a recessive lethal gene on a different chromosome. The Tal gene is not lethal in the heterozygous state but, when homozygous, causes the death of all embryos at 10 to 14 days of gestational age (24). This demonstration in mammals of a lethal epistatic interaction, which is the interaction between genes on different chromosomes, provides a useful system in which to study gene interaction during development

Molecular analysis has delineated the major regions of the rat MHC on the basis of restriction fragment length polymorphisms (RFLPs) (13, 22, 25). There are approximately the same number of class I-hybridizing fragments of DNA as in the mouse (26), despite the much lower level of serological polymorphism in the rat (3). The class II loci have not been examined in any detail yet, but there is a "hotspot" of recombination in the RT1.H region.

The biochemical comparisons among the rat, mouse, and human MHC class I and class II antigens are summarized in Table 1. The amino acid sequences of the rat class I and class II antigens are more homologous to those of the mouse than to those of the human, although both levels of homology are fairly high. The homology among antigens encoded by the same class I locus is the same in the rat and the mouse, and both are lower than in the human. The homology between antigens encoded by different class I loci of the same haplotype is much higher in the rat than in the mouse or the human, whereas the interlocus homology for the class II antigens is approximately the same for all three genuses. When one compares the rat with the mouse and the human the most striking difference is in the number of serologically defined class I and class II antigens. This difference has been documented most extensively for the class I antigens in both inbred (3) and wild (27) populations; it has been less extensively studied for the class II antigens. The class I and class II antigens present in both the inbred and wild populations are serologically and functionally indistinguishable, and there is a high degree of linkage disequilibrium among the loci in the MHC of the rat (27).

The difference between the rat and the mouse and human in the serological polymorphism of their class I antigens stands in contrast to the similarity of their RFLP patterns (20 to 36 class I-hybridizing fragments) (3, 22, 25). This observation might reflect a similarity in the total number of class I genes in all three genuses but a difference in the number of functional genes. The situation with the class II loci in the rat appears to be the same: their serological polymorphism is very low but their RFLP is high (3, 12). Thus, the rat is an extremely useful animal in which to study the control of the functional activity of MHC loci and the biological consequences thereof.

The limited MHC antigen polymorphism in the rat raises the question of what the biological significance of MHC polymorphism is (28). Neither the host defense mechanisms nor the reproductive capacity of the rat appear to differ from those of the mouse and the

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human, and the rat has certainly prospered in an otherwise hostile environment (6). Current thinking assigns a central role to class I antigens in the presentation of foreign antigens to the host immune system and to class II antigens in the recognition of foreign antigens. If these are, indeed, the primary functions of the MHC antigens, then either the specificities of their antigen-recognizing structures are much broader than those of the antibody combining sites or the extent of their antigen-recognition repertoire is not reflected in their serological polymorphism. There is also the relevant, and intriguing, observation that the MHC polymorphism in the protochordate Botryllus is the same as that in the mouse and the human (29). Why? Only more extensive structural studies of MHC antigens at both the protein and DNA levels will provide the crucial insights into the biological significance of MHC antigen polymorphism.

Transplantation

The rat is the animal most often used in organ transplantation studies: its size makes surgical procedures feasible, provides large amounts of cells and serum, and allows serial biopsies of the transplanted organ to assess the rejection process. The advances in rat immunogenetics over the past two decades have enhanced considerably its usefulness in transplantation research. The rejection times of various organs in different strain combinations have been documented (5), and the roles of the different MHC and non-MHC antigens in this process (30) have been examined by the use of different combination of inbred, congenic, and recombinant strains. Such transplantation studies have been done with skin (7, 30), kidney (31), heart (32), bone marrow (33), liver (34), small bowel (35, 36), pancreas (37), and brain (38, 39). There are four major areas of current interest in experimental transplantation research, and the rat is the crucial animal in each of them: allotransplantation of the small bowel, heart, and liver; neural transplantation; xenografting; and reproduction.

Allografting. In systemic allotransplantation, grafting of the small bowel is the most pressing area of study (35, 36). Loss of function in this organ occurs in a variety of situations and at all stages of life: for example, congenital abnormalities, necrotizing enterocolitis, mesenteric artery thrombosis, and trauma. The problems encountered include the proper preservation and restoration of the physiological function of this delicate organ. The immunological problems are those of the host-versus-graft reaction by the recipient's immune system and the graft-versus-host reaction by the lymphoid tissue in the Peyer's patches of the graft. In this sense, small bowel grafting presents the same type of tissue matching problems as bone marrow grafting, but the offending T cells cannot be removed from the bowel graft as easily as they can from the bone marrow graft.

Two other important areas of research in allografting are heart grafting and liver grafting. The most critical issue in the long-term survival of cardiac transplant patients is the development of atherosclerosis in the coronary arteries of the transplant (40). In humans, this process can lead to the loss of the transplant in 5 to 7 years, so an understanding of its pathogenesis will provide a cogent insight into its therapy. In human liver transplantation, the role of histocompatibility (HLA) matching in the survival of the transplant has not been clarified, and there is the suggestion that under certain circumstances matching can reduce the survival of the graft (41). The liver transplantation model has been well developed in the rat (34), and it should provide the appropriate system in which to explore these questions.

Neural transplantation. The rat has been an important animal in the study of allogeneic and xenogeneic neural transplantation. Embryonic neural tissue can be transplanted into neonatal and adult brains

where it can mature and integrate into the host brain. Both allografts and xenografts can survive for prolonged periods, but they are always susceptible to immune rejection either spontaneously or after challenge by related antigens or by mechanical trauma to the central nervous system (38). In the rejection process, however it is precipitated, the host astrocytes are induced to express MHC class I and class II antigens, and the control of such expression may be central to the acceptance of the neural transplant. Cyclosporine A can effectively prolong neural grafts (42). Recent studies in humans (43) suggest that grafts of neuroectodermal origin can be performed, but such grafts have not yet proven to be clinically useful for any significant period of time. The critical factors that affect the success of a neural transplant are the technique and site of the transplant, the amount of disruption of the blood-brain barrier, the size and source of the donor tissue, the vascularization of the transplant, the age of the host and of the donor at the time of transplantation, and the immunogenetic difference between host and donor.

Studies in rats have shown that such transplants can reduce cognitive defects due to frontal cortex lesions (44), improve impairment of motor function in aged animals (45), and make functional connections in an allogeneic or xenogeneic setting (46). These studies are also providing insight into the immunological status of the brain and the immune reactivity in this organ and into the pathogenesis of focal neurodegenerative diseases (38).

The potential value of neural grafts in clinical medicine lies in replacement of damaged neural circuits and in the replacement of cells making chemicals that modulate neural function. Neural circuit replacement might be used to treat trauma in adults and congenital neurological defects in children, and it is in the latter that long-term possibilities for the therapeutic use of neural grafting lie. The use of transplanted cells as a substitute for chemical replacement therapy is complicated by the fact that many of the diseases causing such deficits may have an autoimmune basis, so the transplanted cells themselves may fall victim to the underlying disease process. Much basic work must be done to clarify the immunological and neurophysiological aspects of neural transplantation, the development of specific immunosuppressive regimens for neural transplants, and the pathogenesis of the neurodegenerative diseases for which it might be used as therapy. The effort is worthwhile, since transplantation of tissue into the brain is one of the most promising approaches to have come from experimental neurobiology as potential therapy for a variety of disorders involving damage to the central nervous system. Finally, the use of neural xenotransplants in humans is a distinct possibility (38), and the ethical dilemmas raised by this procedure must be examined.

Xenografts. The use of grafts from animals of different families and genuses, xenografting, has been explored sporadically (47) and has recently had a resurgence because of the interesting basic immunological questions that it raises and because of the possibility of the use of such grafts as neural transplants (38) and as temporary expedients ("bridging grafts") in humans.

Each xenograft system has its own peculiarities (47): thus, it is not possible, at the present time, to generalize about the nature of the immune response to xenografts. In order to explore systematically the immunobiology and immunogenetics of xenografting, three areas of resarch should be developed. First, xenoantigens should be identified and characterized. The relative immunogenicity of various xenografts should be studied in one donor-recipient combination in order to develop a coherent body of knowledge that can serve as a paradigm for other systems. The rat-mouse combination will be the most useful one to study initially, because both species are immunologically and genetically well defined. This research should explore (i) the possible existence of unique xenoantigenic systems, (ii) the role of donor MHC antigens in eliciting an immune response to the

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xenograft, (iii) the cumulative effect that weak antigenic systems have in xenograft rejection, and (iv) the genesis and nature of "natural" or "preformed" antibodies. As an extension of this line of work, the role that the evolutionary distance between donor and recipient plays in the magnitude of the immune response to the xenograft should be examined. Second, the immune response to the xenograft should be analyzed systematically and in detail, including an investigation of the origin and specificities of preformed antibodies. The latter study may provide some insight into methods for controlling their formation. Third, the mechanism of xenograft rejection should be compared to that of allograft rejection to determine whether the major differences between them are qualitative or quantitative.

Reproductive immunology and genetics. This area has as its central theme the mechanism by which the fetal allograft survives (48). The rat is an important experimental animal for examining the nature of the trophoblast antigens and the genetic control of their expression. The allele-specific, class I transplantation antigens are not expressed on the trophoblast surface in allogeneic pregnancies, but they are on the surface in syngeneic pregnancies; in both types of pregnancies, they are present in the cytoplasm (18). The Pa antigen is expressed on the trophoblast surface and in the trophoblast cytoplasm in both allogeneic and syngeneic placentas; class II antigens are not expressed in either type of placenta (18). This differential antigen expression may be an important factor in the maternal acceptance of the allogeneic placenta. Recent work shows that all of the class I antigens expressed in the placenta are of paternal origin, and this is the first example at the antigen level of genomic imprinting, which is a critical process in reproductive genetics (49). The very low level of MHC antigen polymorphism in the rat is crucial to the discrimination needed for these types of studies.

Recessive lethal genes are important causes of fetal death in experimental animals, and they may play an important role in recurrent spontaneous abortion in humans (48, 50). The grc in the rat, as discussed above, provides a unique model system in which to study these effects. This area of research is an important bridge between the aspects of reproduction of primary interest in the field of transplantation and the broader field of developmental genetics.

Risk Assessment for Potential Carcinogens

The rat has been used frequently for prediction of the effects of chemicals on humans (51). For studies of teratogenesis, the advantages of the rat include the ease of counting corpora lutea when assessing the effects of chemicals on ovulation and implantation (52), a large litter size, a short gestation period, and a well-studied embryology. However, the susceptibility and sensitivity of rats to particular teratogenic agents may be low when compared with the mouse and the rabbit (52), and there are significant differences from man in the effects of chemicals on the fetus (53). In mutagenesis studies, the rat appears to offer little inherent advantage over several other species (54). It is in the field of carcinogenic risk assessment that the rat has played a prominent role and will continue to do so.

Prediction of carcinogenicity for a given chemical is a major concern for government, the chemical industry, and the public. The development of cancer usually involves, at some stage, an agent or agents foreign to the cell—including xenobiotics, radiation, and oncogenic viruses. Carcinogenesis is a multistep process frequently involving a genotoxic (DNA-altering) step resulting in the alteration of cell division, growth, and differentiation (55). Different chemicals, including some with similar structures, may work by different mechanisms, and the cellular differences among tissues further complicate the process. Often one, or sometimes more, specific

activated metabolite of a chemical may be the ultimate carcinogen (56); hence, different tissues and species of animals may respond differently to any given chemical based on their inherent metabolic patterns. The many unknown aspects of the induction of cancer, the long latency period between exposure and overt disease, and the potential for carcinogenesis at low doses of chemicals have made risk assessment an extremely difficult exercise.

Ultimately, it is epidemiologic studies of humans that will confirm the ability of an agent to cause human cancer (57), but such studies are usually performed only after exposure of large populations. This situation has led to the development of carcinogenic risk assessment methodologies that utilize nonhuman test systems (53). Assessment of carcinogenicity involves long-term dietary, parenteral, or topical application of the chemical to various mammalian species (58). The rat features prominently in such studies because of a favorable combination of small body size, ease of breeding, and relatively low spontaneous tumor rates. The choice of the strain of rats that is used is important in view of the variation in spontaneous tumor rates and different responses to chemicals among inbred strains (58). More recently, it has become apparent that such longterm bioassays may occasionally produce conflicting results, as occurred initially with vinylidene chloride (59, 60), or may be used with agents such as arsenic that exhibit sufficient evidence of carcinogenicity in humans but limited evidence in animal tests (60). Furthermore, because the mechanisms of chemical carcinogenesis have become better understood and the potential for simultaneous exposure to several chemicals has become apparent, chemicals may in the future be assessed for their activity at different stages of the multistep carcinogenic process (61).

The long-term application of a test chemical to animals will continue to be the fundamental method of carcinogenic risk assessment because short-term, and particularly in vitro, tests cannot mimic all of the aspects of animal metabolism and physiology (62). The long-term bioassays should be done over a large part of the life span of the species, starting in utero, in order to eliminate false negative results due to the prolonged latency of carcinogenic effects. In this respect, the rat is a suitable experimental animal because of its relatively short life span.

In view of the important role played by metabolic enzymes in activating chemicals to reactive carcinogens, the question arises as to whether the rat is metabolically an appropriate substitute for humans. Crouch and Wilson (63), using the National Cancer Institute long-term bioassay data and a mathematical formula for carcinogenic potency, demonstrated that the ratio of potency between humans and rats was, on average, within a fivefold range; however, for a given chemical it varied from 1500:1 to 0.02:1. The range of potencies was less divergent between mice and rats, although Bernstein et al. (64) have argued that this lack of divergence may be a statistical artifact inherent in the long-term bioassays. Purchase (65) analyzed 250 chemicals for carcinogenicity in rats and mice based on data from the National Cancer Institute, International Agency for Research on Cancer, and U.S. Public Health Service, and his analysis indicated that a chemical carcinogenic in one species had a 15% chance of not being carcinogenic in the other. These data emphasized the importance of testing chemicals in more than one species in long-term bioassays (58). The rat is clearly an appropriate choice for one of these species because so much is known about its metabolic and physiological patterns and because various classes of chemicals are carcinogenic for rats (53, 59).

Recent studies on mechanisms of chemical carcinogenesis have demonstrated deficiencies in long-term animal carcinogenesis testing when it is used as the sole assessment criterion, because problems may occur with chemicals that are carcinogenic but that cause only moderate tumor incidence in a given tissue in different

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species (59). Certain chemicals, notably epigenetic (non-DNA altering) ones, may affect a particular stage of the multistep carcinogenic process initiated by another chemical without being themselves active in a long-term bioassay when tested alone. These facts, together with the increasing costs and slowness of long-term testing, have forced consideration of assays that require less time. Weisburger and Williams (59) outlined a decision-point approach to testing whereby chemicals might be analyzed in four increasingly complex classes of carcinogenicity assessment. These classes are as follows: (i) Analysis of the structure of the chemical. This analysis considers the reactivity of the chemical and its metabolites based on structure (66). (ii) Short-term tests in vitro. A battery of tests is used including prokaryotic and mammalian mutagenesis systems and studies of direct effects on DNA and chromosomes. (iii) Limited bioassays in vivo. The formation of preneoplastic lesions or rapid tumor induction is assessed in selected species. (iv) Long-term bioassays in vivo. A positive result in these studies is increased overt tumor formation or tumor-induced death of the animal.

For limited bioassay procedures, the induction of breast cancer in female Sprague-Dawley rats and the induction of altered foci in the rat liver may be useful. Cellular and subcellular preparations from rat livers are also commonly used for metabolic activation of chemicals in short-term carcinogenesis and mutagenesis tests (67, 68). Coculture of rat hepatocytes with liver epithelial-type cells has been reported to sustain high levels of hepatocyte, carcinogen-metabolizing cytochrome P-450 enzymes (69). Such procedures may extend the utility of in vitro hepatocyte cell lines in toxicity testing. The comprehensive assessment proposal of Weisburger and Williams (59) is not an established procedure (58), but rather illustrates potential future directions for carcinogenic risk assessment. The rat plays an important role in short-term in vitro tests and in limited in vivo bioassays.

The rat has been the most frequently studied species in the in vivo bioassay system of altered liver-focus induction. Research into the cellular events in the course of chemically induced tumor formation has characterized many of the changes that precede malignancy (70, 71). Cell populations affected by the carcinogen generally appear as characteristically altered foci detectable by sensitive immunohistochemical reactions, and they appear much earlier than tumor formation. Induction of such foci is not an unequivocal indicator of ultimate malignancy, and their significance in the development of malignancy is debated (70). Nevertheless, this assay has been proposed as a limited in vivo bioassay system in carcinogenicity assessment (59, 70, 72). Pereira and Stoner (73) have reported that the rat liver focus assay exhibited greater sensitivity and fewer false negatives that the strain A mouse lung adenoma assay [some limitations of which are discussed in (53)] in detecting genotoxic carcinogens. Parodi et al. (74) concluded that, at least for a small group of chemicals active predominantly in the liver, assays for liver focus and nodule formation were as accurate, and possibly more accurate, in detecting carcinogenicity than was the Ames test. Preneoplastic lesions have been studied in tissues other than the liver, but a systematic evaluation of their use in bioassays has not been reported (7.5). In view of the large amount of knowledge concerning liver focus formation in the rat (72), it is clear that this species will feature prominently in potential bioassay applications. Strains of rats carrying the growth and reproduction complex (grc), which is linked to the MHC, exhibit enhanced focus formation compared to wild-type rats when exposed to chemical carcinogens (21, 76), and they are candidates for development of highly sensitive liver-focus bioassays.

In the future of carcinogenicity assessment, there is increasing interest in subdividing the carcinogenic process and studying individual stages. As more is learned about the multistep mechanisms, it

may be possible to develop assays for the identification of agents that predispose cells to malignancy at specific steps in the process; one such system has already been described for the rat (61). With the increasing emphasis on genetic mechanisms in carcinogenesis, the availability of randomly bred, outbred, inbred, and congenic strains of rats (3–5) will make this species even more useful in risk assessment as well as in studies on the basic mechanisms of carcinogenesis.

Cardiovascular Diseases

The extensive body of knowledge regarding nutrition, endocrinology, metabolism, and physiology; the detailed studies on anatomy and histology; and the convenient size of the rat make it a particularly useful experimental animal for cardiovascular research. Reproducible, genetically determined abnormalities have been discovered in rat populations that have proven useful in examining the cardiovascular effects of hypertension, obesity, diabetes, and other metabolic diseases (4, 77) and a variety of congenital abnormalities of the cardiovascular system (78).

Early studies indicated that this species was quite different from humans in its serum lipid and lipoprotein constitution and that it was very difficult to produce sustained hyperlipidemia in the rat (79). Until approximately 1950, many attempts to produce atheromatous lesions in the rat had failed in spite of the extensive knowledge about the effects of nutritional manipulation in this species. Then, in the early 1950s simultaneous reports from three laboratories indicated that this resistance could be overcome under the proper experimental conditions (80-82). Each study was designed to capitalize on the newly emerging concepts of risk factors for atherosclerosis, and each utilized rats whose resistance to atherogenesis was diminished by unique ways of producing hypercholesterolemia. Hartroft and his colleagues (80) and Wissler and his group (81) fed rats special diets designed to raise their blood cholesterol levels and then induced hypertension or renal disease or fed the rats chemicals such as propyl thiouracil and sodium cholate. Malinow and his associates (82) utilized particularly potent dietary imbalances plus thyroid-depressing agents to induce atherosclerotic lesions. Some of the major findings emerging from these studies were the greater involvement of the coronary arteries than of the aorta, the location of the aortic lesions in the proximal part of the

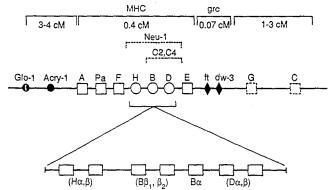


Fig. 1. The major histocompatibility complex of the rat. \square , Class I major (classical) transplantation antigens; the dashed squares, the class I medial transplantation antigens; \bigcirc , class II antigens; \bigcirc , loci controlling polymorphic proteins (Glo-1, glyoxylase I; Acry-1, α -crystallin-1); and \bigcirc , the loci of the gr (ft, fertility; dw-3, dwarf-3). The loci indicated by brackets have been mapped to the regions indicated (Neu-1, neuraminidase-1; \square , complement components). The evidence for this mapping is presented in (3, 12, 13). A cytogenetic study (15) has placed the MHC on chromosome 14 of the rat.

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Table 1. Amino acid homologies between MHC class I and class II antigens of the rat and those of the mouse and the human (3, 14, 101).

| | | | | Percentage l | Approximate number of | | | | |
|-----------------|---|----------------------------|----------------------|--------------------------------|---------------------------------------|--|--------------------------|---------------------------|-----------------------------|
| Type Comparison | Rat con | npared to | Allelio | serologically defined alleles* | | | | | |
| | | Mouse | Human | Rat | Mouse | Human | Rat | Mouse | Human |
| Class I | Signal peptide α ₁ domain α ₂ domain α ₃ domain Transmembrane- | 85 71–73 71–78 87 | 50 68 67 72 | 68–73 (A) 97–98 (A:E) | 32–69 (K) 34–57 (D) 36–69 (K:D) | 85-95 (<i>A</i>) 93 (<i>B</i>) 79-85 (<i>A</i> : <i>B</i>) | 12 (A) 2 (E) 4 (C) | 92 (K) 63 (D) 2 (L) | 24 (A) 52 (B) 11 (C) |
| Class II | cytoplasmic domain | 38–46 80–91 | 40 73–81 | 56–59 (B:D) | 52-60 (A:E) | 64–66 (DR:DQ) | 10 (B,D) | 74 (A) 72 (E) | 20 (DR) 9 (DQ) 6 (DP) |

^{*}Locus or loci compared given in parentheses.

ascending thoracic aorta, and the additive influence of multiple risk factors (83). In subsequent studies this model was used to define the influences of various kinds of food fats (84) and of metabolic manipulations (85) and to delineate the ultrastructural features of these lesions (86). In the latter studies, the lesions resemble the foam cell lesions of the rabbit and of other animals in which the blood cholesterol had very high values and in which there was some degree of endothelial injury (87). The availability of a wide variety of genetically defined strains of rats will now allow studies such as these to be designed to explore the genetic basis of the various risk factors involved in atherogenesis.

Two inbred strains of rats are particularly useful for studying the pathogenesis of cardiovascular diseases: the SHR (spontaneously hypertensive) strain (88) and the BB strain, which spontaneously develops insulin-dependent diabetes mellitus (89). The SHR rats develop hypertension that increases with age; is more severe in males; leads to cerebral, myocardial, vascular, and renal lesions; and is responsive to antihypertensive agents. The hypertension is a genetically transmitted trait that is most likely polygenic, and in well-maintained colonies all of the animals develop hypertension between 5 and 10 weeks of age. The inbred, genetically related WKY strain is often used as the normotensive control for the SHR strain. Stroke-prone (90) and obese (91) substrains of the SHR strain have been developed, but they are difficult to select and maintain because these phenotypic traits most likely have a polygenic basis. The onset of diabetes in the BB rats is rapid, occurs around 90 days of age, affects both males and females, and is under polygenic control, one component of which is linked to the MHC. The clinical syndrome consists of hyperglycemia, hypoinsulinemia, ketosis, polyuria, glycosuria, and weight loss. Pathologic examination shows selective inflammatory destruction of the beta cells of the islets of Langerhans in the pancreas, and the inflammatory process has a substantial immunological component.

Behavior

The rat has been used for studies in behavior since the turn of the century, and a substantial literature has emerged from these studies (92, 93). The investigation of the hereditary and environmental aspects of learning began with the introduction of maze experiments by Small (94) and led to the development of "maze-bright" and "maze-dull" lines of rats by selective breeding (95). Various emotional characteristics have been developed in rats by selective breeding (93, 96), and the role of different areas of the brain in behavior has been investigated by stimulation and by extirpation experiments (44, 45, 97). Finally, the effects of aging (93, 98) and of various pharmacological agents, including alcohol (99) and narcotics (100), on behavior have been explored.

These studies have provided insights into behavior and into its anatomic and physiologic basis and have led to the development of the field of experimental psychology. However, the lines of rats used were not developed according to the standard rules of genetic inbreeding, and they generally led, at best, to populations with a restricted genetic composition, relative to a randomly breeding population of rats, in which a certain phenotypic characteristic was prominent. This situation has complicated the more detailed genetic interpretation of much of the experimental literature on behavior, and it is particularly acute when examining the relative roles of heredity and environment in learning. One possible approach to developing appropriate strains of rats for behavioral studies may be to select partially inbred rats for their behavioral characteristics and then to breed them for these traits in the context of a mating scheme that would also continue the inbreeding.

Concluding Remarks

The rat is a major experimental animal in all fields of biomedical research and technology, and studies with it have provided much basic and applied knowledge. Its greatest utility has been in those fields broadly classified as experimental pathology and experimental surgery. The extensive work done on the immunology and genetics of the rat in recent decades has greatly enhanced its utility and has contributed substantially to the body of knowledge in immunogenetics. As the constraints on the use of larger animals grow, the rat should provide an excellent alternative to their use. Such a change would also have the advantage of allowing more sophisticated studies to be designed, since so much is known about the biology of the rat, and this would greatly enhance the value of the experiments done.

REFERENCES AND NOTES

- 1. H. H. Donaldson, J. Acad. Nat. Sci. Philadelphia 15, 365 (1912); W. E. Castle,
- Proc. Natl. Acad. Sci. U.S.A. 33, 109 (1947).
 R. D. Owen, Ann. N.Y. Acad. Sci. 97, 37 (1962); J. Palm, ibid., p. 57; O. Stark, V. Kren, B. Frenzl, Folia Biol. (Prague) 13, 85 (1967); B. Heslop, Aust. J. Exp. Biol. Med. Sci. 46, 479 (1968); H. W. Kunz and T. J. Gill III, J. Immunogenet. 1, 413 (1974); T. Natori et al., Transplant. Proc. 11, 1568 (1979).
- 3. T. J. Gill III, H. W. Kunz, D. N. Misra, A. L. Cortese Hassett, Transplantation 43, 773 (1987).
- 4. T. J. Gill III, Physiologist 28, 9 (1985).
- I. B. Calhoun, The Ecology and Sociology of the Norway Rat (Department of Health, Education and Welfare, Bethesda, MD, 1962); R. Robinson, Genetics of the Norway Rat (Pergamon, New York, 1965); Inbred and Genetically Defined Strains of Laboratory Animals, part 1, Mouse and Rat, P. L. Altman and D. D. Katz, Eds. (Federation of American Societies for Experimental Biology, Bethesda, MD,

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1979); M. F. W. Festing, Inbred Strains in Biomedical Research (Oxford Univ. Press, New York, 1979); Spontaneous Animal Models of Disease, E. J. Andrews, B. C. Ward, M. H. Altman, Eds. (Academic Press, New York, 1979), vols. 1 and 2; The Laboratory Rat, H. J. Baker, J. R. Lindsey, S. H. Weisbroth, Eds. (Academic Press, New York, 1979), vols. 1 and 2; T. J. Gill III, Am. J. Pathol. 101, 521 (1980); M. F. W. Festing, in Immunologic Defects in Laboratory Animals, M. E. Gershwin and B. Merchant, Eds. (Plenum, New York, 1981), pp. 267–283.
T. Y. Canby and J. L. Stanfield, Natl. Geogr. 15, 60 (1977)

- E. Gunther and O. Stark, in The Major Histocompatibility System in Man and Animals, D. Goetze, Ed. (Springer-Verlag, New York, 1977), pp. 207–253.
- M. Aizawa and T. Natori, Major Histocompatibility Complex of the Rat Rattus norvegicus (Kokoku Printing Co. Ltd., Sapporo, 1988).
 J. C. Howard, Metabolism 32, 41 (1983).

- T. J. Gill III and H. W. Kurz, Eds., International Workshops on Alloantigenic Systems in the Rat. I. Transplant. Proc. 10, 271 (1978); II. ibid. 11, 1549 (1979); III. ibid. 13, 1307 (1981); IV. ibid. 15, 1533 (1983); V. ibid. 17, 1793 (1985); VI. ibid. 19, 2983 (1987); VII. ibid. 21, 3239 (1989).
- 11. Rat Newsletter is published by the Department of Pathology, University of
- Pirtsburgh School of Medicine, Pittsburgh, PA 15261.

 12. J. W. F. Watters, J. Locker, H. W. Kunz, T. J. Gill III, Immunogenetics 26, 220 (1987); H. Fujii et al., ibid. 29, 217 (1989).

 13. A. L. Cortese Hassett et al., Transplant. Proc. 21, 3244 (1989).

14. J. Klein, Natural History of the Major Histocompatibility Complex (Wiley-Interscience, New York, 1986).

- New York, 1986).
 T. Oikawa et al., Jpn. J. Genet. 58, 327 (1983).
 D. N. Misra, H. W. Kunz, T. J. Gill III, Immunogenetics 26, 204 (1987); D. N. Misra, H. W. Kunz, A. L. Cortese Hassett, T. J. Gill III, ibid. 25, 35 (1987); D. N. Misra, H. W. Kunz, T. J. Gill III, Transplant. Proc. 21, 3271 (1989).
 A. M. Ghani, T. J. Gill III, H. W. Kunz, D. N. Misra, Transplantation 37, 187 (1984); A. M. Ghani, H. W. Kunz, T. J. Gill III, ibid. 11, 503; T. A. Macpherson, H. N. Ho, H. W. Kunz, T. J. Gill III, ibid. 41, 392 (1986); H. N. Ho, T. A. Macpherson, H. W. Kunz, T. J. Gill III, ibid. 41, 392 (1986); H. N. Ho, T. A. Macpherson, H. W. Kunz, T. J. Gill III, ibid. 41, 392 (1986); H. N. Ho, T. A. Macpherson, H. W. Kunz, T. J. Gill III, ibid. 41, 392 (1986); H. N. Ho, T. A. Macpherson, H. W. Kunz, T. J. Gill III, ibid. 41, 392 (1986); H. N. Ho, T. A. Macpherson, H. W. Kunz, T. J. Gill III, ibid. 41, 392 (1986); H. N. Ho, T. A. Macpherson, H. W. Kunz, T. J. Gill III, ibid. 41, 392 (1986); H. N. Ho, T. A. Macpherson, H. W. Kunz, T. J. Gill III, ibid. 41, 392 (1986); H. N. Ho, T. A. Macpherson, H. W. Kunz, T. J. Gill III, ibid. 41, 392 (1986); H. N. Ho, T. A. Macpherson, H. W. Kunz, T. J. Gill III, ibid. 41, 392 (1986); H. N. Ho, T. A. Macpherson, H. W. Kunz, T. J. Gill III, ibid. 41, 392 (1986); H. N. Ho, T. A. Macpherson, H. W. Kunz, T. J. Gill III, ibid. 41, 392 (1986); H. N. Ho, T. A. Macpherson, H. W. Kunz, T. J. Gill III, ibid. 41, 392 (1986); H. N. Ho, T. A. Macpherson, H. W. Kunz, T. J. Gill III, ibid. 41, 392 (1986); H. N. Ho, T. A. Macpherson, H. W. Kunz, T. J. Gill III, ibid. 41, 392 (1986); H. N. Ho, T. A. Macpherson, H. W. Kunz, T. J. Gill III, ibid. 41, 392 (1986); H. N. Ho, T. A. Macpherson, H. W. Kunz, T. J. Gill III, ibid. 41, 392 (1986); H. N. Ho, T. A. Macpherson, H. W. Kunz, T. J. Gill III, ibid. 41, 392 (1986); H. N. Ho, T. A. Macpherson, H. W. Kunz, T. J. Gill III, ibid. 41, 392 (1986); H. N. Ho, T. A. Macpherson, H. W. Kunz, T. J. Gill III, ibid. 41, 392 (Macpherson, H. W. Kunz, T. J. Gill III, Am. J. Reprod. Immunol. Microbiol. 13, 51
- 18. A. Kanbour et al., J. Exp. Med. 166, 1861 (1987).
- H. W. Kunz, A. L. Cortese Hassett, T. Inomata, D. N. Misra, T. J. Gill III, Immunogenetics, in press; K. Wonigeit, H. J. Hedrich, E. Gunther, Transplant. Proc. 11, 1584 (1979); W. Stock and E. Gunther, J. Immunol. 128, 1923 (1982).
 H. W. Kunz, T. J. Gill III, B. D. Dixon, F. H. Taylor, D. L. Greiner, J. Exp. Med. 1523 (1982).
- 152, 1506 (1980); T. J. Gill III, S. Siew, H. W. Kunz, J. Exp. Zool. 228, 325 (1983); T. J. Gill III et al., in Immunoregulation and Fetal Survival, T. J. Gill III and T. G. Wegmann, Eds. (Oxford Univ. Press, New York, 1987), pp. 137-155.

 21. K. N. Rao, H. Shinozuka, H. W. Kunz, T. J. Gill III, Int. J. Cancer 34, 113
- (1984); M. Melhem, K. N. Rao, M. Kazanecki, H. W. Kunz, T. J. Gill III, unpublished data.
- 22. A. L. Cortese Hassett, K. S. Stranick, J. Locker, H. W. Kunz, T. J. Gill III, Immunol. 137, 373 (1986); A. L. Cortese Hassett, J. Locker, G. Rupp, H. W.
- Kunz, T. J. Gill III. ibid. 142, 2089 (1989).
 A. G. Knudson, Jr., Cancer Res. 45, 1437 (1985); M. F. Hansen and W. K. Cavenee, ibid. 47, 5518 (1987).
 D. J. Schaid, H. W. Kunz, T. J. Gill III, Genetics 100, 615 (1982).

- M. Palmer, P. J. Wettstein, J. A. Frelinger, Proc. Natl. Acad. Sci. U.S. A. 80, 7616 (1983);
 E. Gunther, W. Wurst, K. Wonigeit, J. T. Epplen, J. Immunol. 134, 1257 (1985)
- L. Hood, M. Steinmerz, B. Malissen, Annu. Rev. Immunol. 1, 529 (1983); M. C. Carroll et al., Proc. Natl. Acad. Sci. U.S.A. 84, 8535 (1987).
 D. V. Cramer, B. K. Davis, J. W. Shonnard, O. Stark, T. J. Gill III, J. Immunol. 120, 179 (1978); E. P. Blankenhorn and D. V. Cramer, Immunogenetics 21, 135 (1985); D. K. Wagener, D. V. Cramer, J. W. Shonnard, B. K. Davis, ibid. 9, 157 (1979
- 28. T. J. Gill III, D. V. Cramer, H. W. Kunz, D. N. Misra, J. Immunogenet. 10, 261
- 29. V. L. Scofield, J. M. Schlumpberger, L. A. West, I. Weissman, Nature 295, 499 (1982). S. M. Katz, D. V. Cramer, H. W. Kunz, T. J. Gill III, Transplantation 36, 463
- (1983); S. M. Katz et al., ibid., p. 96.
- 31. A. Paris and E. Gunther, Immunogenetics 10, 205 (1980); G. D. Majoor and P. J. C. van Breda Vreisman, Transplantation 41, 92 (1986).
 32. D. V. Cramer, CRC Crit. Rev. Immunol. 7, 1 (1987).
- M. Pinto, T. J. Gill III, H. W. Kunz, B. D. Dixon-McCarthy, Transplantation 35, 607 (1983); M. K. Oaks and D. V. Cramer, ibid. 39, 69 (1985); ibid., p. 504; D.
- Leszczynski, R. Renkonen, P. Hayry, Am. J. Pathol. 120, 316 (1985).
 M. Kamada, H. F. F. Davis, D. Wight, L. Culank, B. Roser, Transplantation 35, 304 (1983); N. Karrada, Immunol. Today 6, 336 (1985); S. J. Knechtle, J. A. Wolfe, J. Burchette, F. Sanfilippo, R. R. Bollinger, Transplantation 43, 169 (1987).
- R. L. Kirkman, Transplantation 37, 429 (1984).
 M. D. Lee, H. W. Kunz, T. J. Gill III, D. A. Lloyd, M. R. Rowe, ibid. 42, 235

- M. D. Lee, H. W. Kultz, I. J. Gill III, D. A. Lloyd, M. K. Rowe, total. 42, 259 (1986); D. Shaffer et al., ibid. 45, 262 (1988).
 B. Steiniger, J. Klempnauer, K. Wonigeir, ibid. 40, 234 (1985); M. J. Orloff, A. Macedo, G. E. Greenleaf, B. Girard, ibid. 45, 307 (1988).
 R. D. Lund, K. Rac, H. W. Kunz, T. J. Gill III, ibid. 46, 216 (1988); in Neuroimmune Networks: Physiology and Disease, E. J. Goetzl and N. Spector, Eds. (Liss, New York, in press); Transplant. Proc. 21, 3159 (1989); T. J. Gill III and R. D. Lund, J. Am. Med. Assoc. 261, 2674 (1989).
- S. J. Geyer, T. J. Gill III, H. W. Kunz, E. Moody, Transplantation 39, 244 (1985); M. K. Nicholas et al., J. Immunol. 139, 2275 (1987)
- B. F. Urersky et al., Circulation 76, 827 (1987); E. A. Pascoe et al., Transplantation 44, 838 (1987).

- 41. B. H. Marcus et al., Transplantation 46, 372 (1988).
- 42. H. Inoue et al., Neurosci. Lett. 54, 85 (1985)
- I. Madrazo et al., N. Engl. J. Med. 316, 831 (1987).
 R. Labbe, A. Firl, Jr., E. J. Mufson, D. G. Stein, Science 221, 470 (1983).
- 45. F. H. Gage, S. B. Dunnett, U. Stenevi, A. Björklund, ibid., p. 966.
- 46. H. K. Klassen and R. D. Lund, Exp. Neurol. 102, 102 (1988).
- H. Auchincloss, Jr., Transplantation 46, 1 (1988).
 T. J. Gill III and C. F. Reperti, Am. J. Pathol. 95, 465 (1979); T. J. Gill III, in The Physiology of Reproduction, E. Knobil and J. Neill, Eds. (Raven, New York, 1988), pp. 2023–2042; T. G. Wegmann and T. J. Gill III, Eds., Immunology of Reproduction (Oxford Univ. Press, New York, 1983); D. A. Clark and B. A. Croy, Eds., Reproductive Immunology 1986 (Elsevier, Amsterdam, 1986); T. J. Gill III and T. G. Wegmann, Eds., Immunoregulation and Fetal Survival (Oxford Univ. Press, New York, 1987).

 49. M. A. H. Surani, S. C. Barton, M. L. Norris, Biol. Reprod. 36, 1 (1987).

 50. T. J. Gill III, Am. J. Reprod. Immunol. Microbiol. 15, 133 (1987).

 51. C. Maltoni and I. J. Selikoff, Eds., Ann. N.Y. Acad. Sci. 543, 1 (1988); F. Feo, P.

- Pani, A. Columbano, R. Garcea, Eds., Chemical Carcinogenesis: Models and Mechanisms (Plenum, New York, 1988).
- H. Tuchmann Duplessis, in Methods in Prenatal Toxicology, D. Neubert, H. J. Merker, T. E. Kwasigroch, Eds. (Thieme, Stuttgart, West Germany, 1977), pp.
- D. B. Clayson, in *Toxicological Risk Assessment*, D. B. Clayson, D. Krewski, I. Munro, Eds. (CRC Press, Boca Raton, FL, 1985), vol. 1, pp. 105–122; *Mutation* Res. 185, 243 (1987)
- S. Venitt and J. M. Parry, Eds., Mutagenicity Testing: A Practical Approach (IRL Press, Oxford, 1984).

55. H. C. Pitot, Cancer Surv. 2, 519 (1983).

J. Miller and E. Miller, in Environmental Carcinogenesis, P. Emmelot and E. Kriek, Eds. (Elsevier, Amsterdam, 1979), pp. 25-50.

- R. Doll and R. Peto, J. Natl. Cancer Inst. 66, 1191 (1981).
 J. Sontag, N. Page, U. Saffiotti, Guidelines for Carcinogen Bioassay in Small Rodents (DHEW Publ. NIH 76-801, National Cancer Institute, Bethesda, MD, 1976), pp. 1–65; E. L. Anderson, in Methods for Estimating Risk of Chemical Injury: Human and Non-Human Biota and Ecosystems, V. B. Vouk, G. C. Butler, D. G. Hoel, D. B. Peakall, Eds. (Wiley, Chichester, United Kingdom, 1985), pp. 405–436; R. Montesano, H. Bartsch, H. Vainio, J. Wilbourn, H. Yamasaki, Eds., Long-Term and Short-Term Assays for Carcinogens: A Critical Appraisal, IARC Scientific Ser. no. 83 [International Agency for Research on Cancer (IARC), Lyon, 1986]; U. Mohr and H.-B. Richter-Reichelm, in Animals in Toxicology Research, I. Bartosek, A. Guaitani, E. Pacei, Eds. (Raven, New York, 1982), pp. 65-70. J. H. Weisburger and G. M. Williams, Science 214, 401 (1981); in Casarett and
- Doull's Toxicology, C. Klaason, M. Amdur, J. Doull, Eds. (Macmillan, New York, ed. 3, 1986), pp. 99–173.

 60. International Agency for Research on Cancer, IARC Monogr. Suppl. 7 (IARC,
- Lyon, 1987), pp. 100–106.
 T. L. Goldswothy and H. C. Pitot, J. Toxicol. Environ. Health 16, 389 (1985).
 H. Greim, U. Andrae, W. Goggelmann, L. Schwarz, K. H. Summer, in Cancer Risks: Strategies for Elimination, P. Bannasch, Ed. (Springer-Verlag, Berlin, 1987),
- pp. 33-46. E. Crouch and R. Wilson, J. Toxicol. Environ. Health 5, 1095 (1979). L. Bernstein, L. S. Gold, B. N. Ames, M. C. Pike, D. G. Hoel, Fund. Appl. Toxicol. 5, 79 (1985).

- I. F. H. Purchase, Br. J. Cancer 41, 454 (1980).
 J. Ashby and R. W. Tennant, Mutat. Res. 204, 17 (1988).
 B. Ames, Science 204, 587 (1979); ______, R. Magaw, L. S. _, R. Magaw, L. S. Gold, ibid. 236, 271
- G. Williams, in Short-Term Tests for Chemical Carcinogens, R. San and H. Stich, Eds. (Springer-Verlag, New York, 1980), pp. 581-609.
- J. M. Begue, C. Guguen-Guillouzo, N. Pasdeloup, A. Guillouzo, Hepatology 4, 839 (1984)
- P. Bannasch, H. Enzmann, H. Zerban, in Cancer Risks: Strategies for Elimination, P. Bannasch, Ed. (Springer-Verlag, Berlin, 1987), pp. 47-64.
 E. Farber, Biochim. Biophys. Acta 605, 149 (1980).
 M. A. Moore and T. Kitagawa, Int. Rev. Cytol. 101, 125 (1986).
 M. A. Pereira and G. D. Stoner, Fund. Appl. Toxicol. 5, 688 (1985).
 S. Parodi, M. Taningher, L. Santi, Anticancer Res. 3, 393 (1983).
 P. Pannasch, Cartingment, 7, 249 (1986).

- P. Bannasch, Carcinogenesis 7, 849 (1986). M. Melhem, K. N. Rao, H. W. Kunz, T. J. Gill III, in Chemical Carcinogenesis: Models and Mechanisms, F. Feo, P. Pani, A. Columbano, R. Garcea, Eds. (Plenum,
- New York, 1988), pp. 485–493.
 77. L. M. Zucker, Ann. N.Y. Acad. Sci. 131, 447 (1965); K. Okamoto, Int. Rev. Exp. Pathol. 7, 727 (1969); H. Wolinsky, Circ. Res. 26, 507 (1970); ibid. 28, 622 (1971); S. Koletsky, Am. J. Pathol. 80, 129 (1975); A. V. Chobanian et al., Diabetes 31 (Suppl. 1), 54 (1982); E. B. Marliss, A. A. F. Sima, A. F. Machooda, in The Etiology and Pathogenesis of Insulin-Dependent Diabetes Mellitus, J. M. Martin, R. M. Ehrlich, F. I. Holland, Eds. (Raven, New York, 1982), pp. 251-274; J. C.

Russell and R. M. Amy, Can. J. Physiol. Pharmacol. 64, 1272 (1986).
 J. G. Wilson and J. Warkany, Pediatrics 5, 708 (1950); J. G. Wilson and J. W. Karr, Am. J. Anat. 88, 1 (1951); J. G. Wilson, C. B. Roth, J. Warkany, ibid. 92, 189 (1953); R. E. Hudson, Cardiovascular Pathology (Williams & Wilkins, Baltimore, MD, 1965), vol. 2, pp. 1647–1653.

 N. Anitschkow, in Arteriosclerosis: A Survey of the Problem, E. V. Cowdry, Ed. (Macmillan, New York, 1933), pp. 271–322; W. C. Hueper, Arch. Pathol. 39, 187 (1945); R. Altschul, Selected Studies on Arteriosclerosis (Thomas, Springfield, IL, 1950), pp. 66-74; L. N. Katz and J. Stamler, Experimental Atherosclerosis (Thomas, Springfield, IL, 1952), pp. 258-261.
80. W. S. Hartroft, J. H. Ridout, E. A. Sellers, C. H. Best, Proc. Soc. Exp. Biol. Med.

- 81, 384 (1952).
- 81. R. W. Wissler, Proc. Inst. Med. Chicago 19, 79 (1952); _ Schroeder, L. Cohen, A.M.A. (Am. Med. Assoc.) Arch. Pathol. 57, 333 (1954).
- M. R. Malinow, D. Hojman, A. Pellegrino, Acta Cardiol. 9, 480 (1954).
 L. C. Fillios, S. B. Andrus, G. V. Mann, F. J. Stare, J. Exp. Med. 104, 539 (1956); G. F. Wilgram, ibid. 109, 293 (1959); S. Naimi, R. Goldstein, M. M. Nothman, G. F. Wilgram, S. Prager, J. Clin. Invest. 41, 1708 (1962); W. J. S. Still and R. M. O'Neal, Am. J. Pathol. 40, 21 (1962).
- C. R. Seskind, M. T. Schroeder, R. A. Rasmussen, R. W. Wissler, Proc. Soc. Exp. Biol. Med. 100, 631 (1959); C. R. Seskind, V. R. Wheatley, R. A. Rasmussen, R. W. Wissler, ibid. 102, 90 (1959).
- M. S. Moskowitz, A. A. Moskowitz, W. L. Bradford, R. W. Wissler, Arch. Pathol. 61, 245 (1956); R. W. Priest, M. T. Schroeder, R. Rasmussen, R. W. Wissler, Proc. Soc. Exp. Biol. Med. 96, 298 (1957).
- 86. I. Joris, T. Zand, J. J. Numari, F. J. Krolikowski, G. Majno, Am. J. Pathol. 113, 341 (1983).
- W. J. S. Still, Anh. Pathol. 89, 392 (1970).
- K. Okamoto, Int. Rev. Exp. Pathol. 7, 227 (1969); "Spontaneously hypertensive (SHR) rats: Guidelines for breeding, care and use," ILAR News 19, G1 (1976).
 A. A. Like, E. Kislauskis, R. M. Williams, A. A. Rossini, Science 216, 644 (1982);
- R. D. Guttmann, E. Colle, F. Michel, T. Seemeyer, J. Immunol. 130, 1732 (1983); M. Angelillo et al., ibid. 141, 4146 (1988).
- K. Okamoto, Circ. Res. Suppl. I (1972), p. 143.
 S. Koletsky, Exp. Mol. Pathol. 19, 53 (1973).

- G. M. Harrington, Behav. Genet. 11, 445 (1981).
 R. E. Wirner and C. C. Wirner, Annu. Rev. Psychol. 36, 171 (1985); G. E. McClearn and T. T. Foch, in Stevens Handbook of Experimental Psychology, R. C.

- Atkinson, R. J. Herrnstein, G. Lindzey, R. D. Luce, Eds. (Wiley, New York, 1988), pp. 677-764.
- 94. W. S. Small, Am. J. Psychol. 11, 80 (1900). 95. R. C. Tyson, 39th Yearb. Natl. Soc. Study Educ. 1, 111 (1940).
- C. S. Hall, in Handbook of Experimental Psychology, S. S. Stevens, Ed. (Wiley, New York, 1951), pp. 304-329; C. Guenaire, G. Feghali, B. Senault, J. Delacour, Physiol. Behav. 37, 423 (1986); R. L. Commissaris, G. M. Harrington, A. M. Ortiz, H. J. Altman, ibid. 38, 291 (1986).
- 97. J. Olds and P. Milner, J. Comp. Physiol. Psychol. 47, 419 (1954); N. E. Miller, Am. Psychol. 13, 100 (1958).
- 98. M. Auroux, Teratology 27, 141 (1983). 99. F. R. George, Pharmacol. Biochem. Behav. 27, 379 (1987); M. A. Linserman, Psychopharmacology 92, 254 (1987).
- T. Suzuki, Y. Koike, S. Yanaura, F. R. George, R. A. Meisch, Jpn. J. Pharmacol.
 45, 479 (1987); T. Suzuki, K. Otani, Y. Koike, M. Misawa, ibid. 47, 425 (1988).
 101. R. Sodoyer et al., EMBO J. 3, 879 (1984); E. D. Albert, M. P. Baur, W. R. Mayr, Eds., Histocompatibility Testing 1984 (Springer-Verlag, New York, 1984), pp. 333–341; "Nomenclature for factors of the HLA system, 1987," Immunogenetics 28, 202 (1989). 391 (1988); A. Radojcic et al., ibid. 29, 134 (1989).
- 102. The work in the authors' laboratories was supported by grants from the National Institutes of Health [CA 18659, HD 09880, HD 08662 (T.J.G. and H.W.K.) and HL 33740, HL 07237, LM 0009 (R.W.W.)]; the Tim Caracio Memorial Cancer Fund, the Beaver County Cancer Society, and the Pathology Education and Research Foundation (T.J.G. and H.W.K.); the New South Wales State Cancer Council and a Yamigawa-Yoshida Memorial International Cancer Study Grant from the International Union Against Cancer (G.J.S.); and the Nutrition and Heart Disease Study (R.W.W.).

Brain

NON-CANCER ENDPOINTS

There are perhaps three considerations that distinguish the health risk evaluation process for cancer endpoints from that for non-cancer endpoints.

- I. While carcinogenic effects are thought to be linear with dose all the way to zero dose, for non-cancer endpoints there exists a threshold dose level below which no adverse health effects occur. This level is typically called the reference dose (RfD), allowable intake chronic (AIC), or no observed adverse effect level (NOAEL).
- II. The contrast between target tissues and the rest of the body is generally more sharply drawn than in carcinogenesis. That is, with non-cancer endpoints the target tissue/organ is often exquisitely susceptible to harm in comparison to other body tissues. Calculation of health effects often calls for the use of physiologically-based pharmacokinetics (PB-PK), so that dose to target tissues can be more closely estimated.
- III. Non-cancer endpoints of injury are much more widely varied and toxin-specific than in cancer, where we believe there is primarily one endpoint, genetic damage, and one outcome, death, that we seek to avoid.

Because of the diversity in non-cancer endpoints, it would be impossible to present an overall survey, and one example will be discussed in some depth. Many of the principles can be extrapolated to other organ systems.

Assessment of Risk for Inhaled Airborne Material

There are many methods available to assess the toxicity of inhaled agents. As summarized below, these tests range from studies in human populations, to measures of lung function in whole animals and histopathological studies of lungs from exposed animals, to *in vitro* measures of pulmonary macrophage function (phagocytosis, viability), etc. The following outline describes various categories of lung injury and types of assays for indicating onset of tissue damage.

- I. Inhalation toxicology data development
 - A. Air monitoring and characterization of collected dusts.
 - B. Epidemiologic studies of previously-exposed populations.
 - C. Clinical trials using controlled exposures of humans.
 - D. Animals, chronic lifetime studies.
 - E. Short term animal bioassays.
 - F. In vitro tests on mammalian or non-mammalian cells.
 - G. *In vitro* examination of molecular interactions with phospholipids, enzymes, nucleic acids, etc.

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II. Mechanisms of lung injury

As a consequence of inhaling toxic gases and particles, a number of pathological processes may be set into motion. None are specific to the lung, but their expression and consequences depend on the unique architecture and physiological role of the respiratory system. Major pathological mechanisms to be discussed are:

- A. Pulmonary edema: Transudation of fluid, altered alveolar stability, impaired gas exchange, and respiratory distress
- B. Inflammation: Irritation leading to mucosal edema, increased mucus production and bronchitis, appearance of neutrophils and inflammatory mediators, increased cell renewal
- C. Immunologic reactions: Asthma, hypersensitivity lung disease, extrinsic allergic alveolitis, anaphylaxis
- D. Altered susceptibility to infection: Cytotoxic and competitive effects on macrophage function, altered mucociliary transport because of changes in cilia or the quantity or rheological character of mucus
- E. Infection: Bacterial, viral, or fungal pneumonia
- F. Proteolysis: Destruction of elastin and collagen leading to emphysema, obstructive lung disease
- G. Fibrosis: Increased connective tissue scarring, excessive collagen, restrictive lung disease
- H. Degenerative changes: Necrosis, calcification, and autolysis
- I. "Pulmonary carcinogenesis: bronchogenic carcinoma, oat cell carcinoma, adenocarcinoma, mesothelioma"

III. Measurement of lung injury

If the lung is injured by inhaled toxic gases and particles, how can the lung injury be detected and quantified? What repertoire of approaches can be used?

Approaches

and

Parameters or Methods:

- A. Mechanical properties (pulmonary function)
 - 1. Resistance
 - 2. Compliance: pressure-volume curves
 - 3. Lung volumes: VC (spirometry), TLC, RV, and FRC (measured by helium dilution, Boyle's law)
 - 4. FEV₁₀ and Full or Partial flow-volume curves
- B. Gas exchange, Adequacy of ventilation, Distribution of ventilation and perfusion
 - 1. Alveolar gas tensions (P_ACO₂, P_AO₂)
 - 2. Arterial p_aCO₂, p_aO₂
 - 3. Ventilation homogeneity: N₂ washout
 - 4. Ventilation (133Xe) or Perfusion (67Ga) scans

- 5. a-A concentration gradients
- 6. Diffusing capacity (carbon monoxide uptake)

C. Measurement of pathology by radiologic techniques

- 1. Atelectasis
- 2. Fibrosis, emphysema, etc.
- 3. Bronchography (Tantalum)
- 4. Focal lesions

D. Mucociliary transport (in vitro and in vivo)

- 1. Nasal
- 2. Airways
- 3. Mucus studies
- 4. Cilia studies

E. Lung lavage parameters

- 1. Surfactant: quantity, composition
- 2. Cell numbers, appearance, and viability
- 3. Cell differential counts: RBC's, PMN's, monocytes, macrophages, lymphocytes
- 4. Proliferation: production of colony-forming units (CFU's) by lavaged cells, uptake of tritiated thymidine
- 5. Mucus constituents
- 6. Biochemistry: albumin, hemoglobin, hydroxyproline, elastase, collagenase, LDH, myeloperoxidase, antiproteases, lysosomal enzymes, active oxygen species, chemotaxins, proliferative factors, and inflammatory mediators (histamine, prostaglandins, leukotrienes)
- 7. In vitro functional assays of macrophage activity: trypan blue dye exclusion, oxygen consumption, ATP levels, lactate production, migration, chemotactic responsiveness, phagocytosis, killing of microorganisms, release of mediators

F. Morphology

- 1. Gough sections
- 2. Reid index
- 3. Morphometric approaches: airway and alveolar dimensions
- 4. Cell types: connective tissue, inflammatory, neoplastic
- 5. Proliferation and cell turnover measures
- 6. Vascular changes

G. Renewal of lung constituents observed in tissue sections

- 1. Metaphase counts colchicine
- 2. Uptake of tritiated thymidine
- 3. Collagen and elastin breakdown and synthesis

H. Lung clearance

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- 1. DTPA-measured lung epithelial permeability
- 2. Clearance of radioactively-labelled inhaled particles
- 3. Clearance of magnetic inhaled particles
- 4. Macrophage motile activity measured by inhaled magnetic particles

I. Microbicidal activity

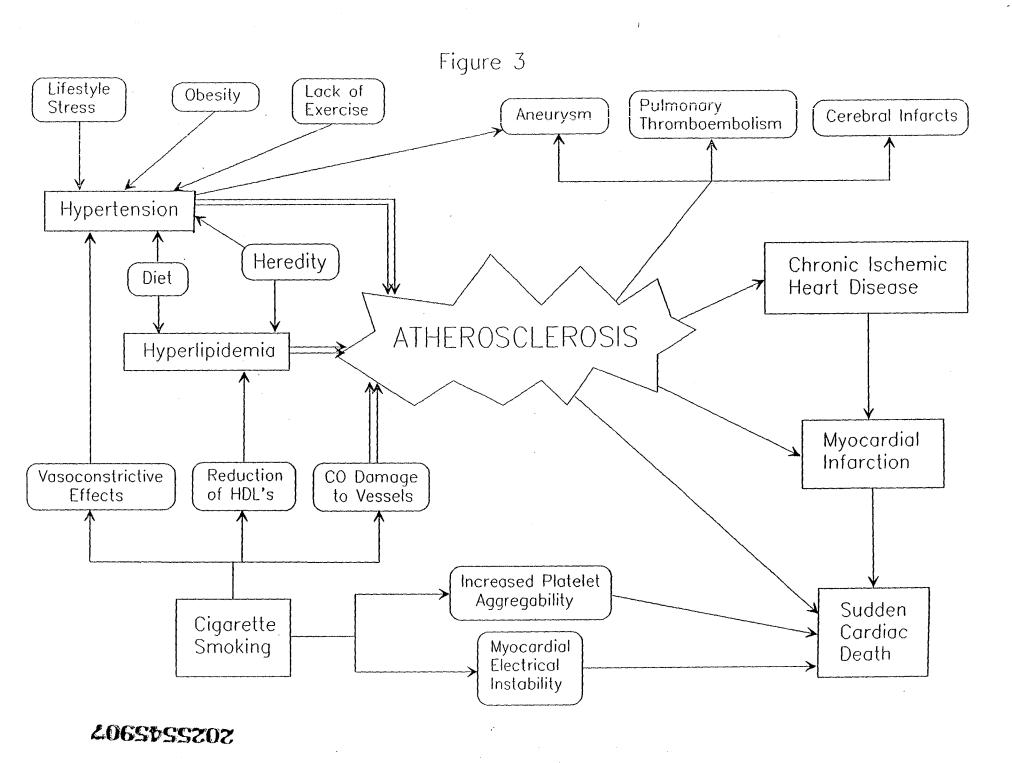
- 1. Recognizable experimental pulmonary infections (morbidity and mortality studies)
- 2. Bacterial aerosol models, in vivo models
- 3. In vitro killing
- 4. Phagocytosis: in vitro and in vivo
- J. Identifying pulmonary carcinogens
 - 1. Experimental pulmonary carcinogenesis (Saffiotti model)
 - 2. Chromosome abnormalities
 - 3. Ames mutagenesis assay
- IV. Bioassays for measuring toxicity of particles and components of particles
 - A. Whole animals
 - B. In vitro cell culture systems
 - C. Cell homogenates
- V. Questions to be considered in the interpretation of data
 - A. Species extrapolation. Are human and animal toxicities equivalent?
 - B. Dose extrapolation. Are the doses given to animals comparable to human exposures?
 - C. Time extrapolation. At what stage is the injury being measured, and how does it compare to the time course of disease development in humans?
 - D. Correlation of disease mechanism with bioassay result
 - E. Specificity of bioassay result: Is result unique to the agent tested? Is the result generalizable to a class of agents? If the agent is a complex mixture, what are the active components? How does the bioassay result agree with disease outcomes in cases where human data are available?

BIBLIOGRAPHY

- I. Mechanisms and Measurement of Lung Injury
 - 1. Allison, A.C. Mechanisms of macrophage damage in relation to the pathogenesis of some lung diseases. In: Respiratory Defense Mechanisms. (Lung Biology in Health and Disease., Monograph 5). Brain, J.D., Proctor, D.F., Reid, L., Eds. Marcel Dekker. New York. 1977. 1075-1102.
 - 2. Brain, J.D. Macrophage damage in relation to the pathogenesis of lung diseases. Environ. Health Perspectives. 35:21-28, 1980.

- 3. Brain, J.D. Toxicological aspects of alterations of pulmonary macrophage function. *Ann. Rev. Pharmacol. Toxicol.* 26:547-565, 1986.
- 4. Doull, J., Klaassen, C.D., and Amdur, M.O. *Toxicology: The Basic Science of Poisons*. New York: MacMillan, 1980. See particularly Chapter 12, "Toxic Responses of the Respiratory System," by D.B. Menzel and R.O. McClellan, and Chapter 24, "Air Pollutants," by M.O. Amdur.
- 5. Fishman, A.P. Pulmonary Diseases and Disorders., volumes 1 and 2. New York: McGraw Hill, 1980.
- 6. Gadek, J.E., Fells, G.A., Crystal, R. Cigarette smoking induces functional antiprotease deficiency in the lower respiratory tract of humans. *Science*. 206: 1315-1316, 1979.
- 7. Harington, J.S., Allison, A.C. Tissue and cellular reactions to particles, fibers, and aerosols retained after inhalation. In: Handbook of Physiology, Section 9: Reactions of Environmental Agents., Falk, H.L., Murphy, S.D., Eds. Bethesda: American Physiological Society, 1977, pp. 263-283.
- 8. Harris, C.C. Pathogenesis and Therapy of Lung Cancer. New York: Marcel Dekker, 1978.
- 9. Janoff, A., Carp, H., Lee, D.K., Drew, R.T. Cigarette smoke inhalation decreases alpha-1-antitrypsin activity in rat lung. Science. 206: 1314-1315, 1979.
- 10. Kirkpatrick, C.H., Reynolds, H.Y., eds. Immunologic and Infectious Reactions in the Lung. (Lung Biology in Health and Disease., Monograph 1). New York: Marcel Dekker, 1976.
- 11. Kuhn, C. III, Senior, R.M. The role of elastase in the development of emphysema. Lung. 155:185-197, 1978.
- 12. Litwin, S.D., Ed. Genetic Determinants of Pulmonary Disease. New York: Marcel Dekker, 1978.
- 13. Snider, G.L., Lucey, E.C., and Stone, P.J. Animal models of Emphysema. Am. Rev. Respir. Dis. 133:149-169, 1986.
- 14. Turino, G.M., Rodriquez, J.R., Greenbaum, L.M., Mandl, I. Mechanisms of pulmonary injury. Am. J. Med. 57:493-505, 1974.
- 15. Wahl, L.M., et al. Collagenase production by lymphokine-activated macrophages. Science. 187: 261-263, 1975.
- White, R., Lin, H.S., Kuhn, C. III. Elastase secretion by peritoneal exudative and alveolar macrophages. J. Exp. Med. 146: 802-808, 1977.
- 17. West, J.B. Pulmonary Pathophysiology: The Essentials. Baltimore: Williams & Wilkins, 2nd edition, 1982.
 - II. Occupational Lung Diseases
- 18. Brooks, S.M., Lockey, J.E., Harber, P., eds. Clinics in Chest Medicine: Occupational Lung Diseases I. Philadelphia: W.B. Saunders Company, 1981.
- 19. Brooks, S.M., Lockey, J.E., Harber, P., eds. Clinics in Chest Medicine: Occupational Lung Diseases II. Philadelphia: W.B. Saunders Company, 1981.
- 20. Dosman, J.A., and Cotton, D.J., eds. Occupational Pulmonary Disease: Focus on Grain Dust and Health. New York: Academic Press, 1977.
- 21. Key, M.M., et al. eds. Occupational Diseases: A Guide to Their Recognition. Dept. of Health, Education, and Welfare Publication No. 77-181, Washington, D.C., U.S. Government Printing Office, 1978. esp. Chapter V, "Diseases of the Airways," by W. Keith, C. Morgan, and N. LeRoy Lapp.
- 22. Kusnetz, S., Hutchinson, M.K., eds. A Guide to the Work-Relatedness of Disease. Dept. of Health, Education, and Welfare Publication No. 79-116, Washington, D.C., U.S. Government Printing Office, 1979.
- 23. Morgan, W.K.C., Seaton, A. Occupational Lung Diseases. Philadelphia: W.B. Saunders Co., 2nd edition, 1984.
- 24. Parks, W.R. Occupational Lung Disorders (2nd ed.). London: Butterworths, 1982.
- 25. Clayton, C.D., and Clayton, F.E. Patty's Industrial Hygiene and Toxicology. Vols. 2A, 2B, 2C: Toxicology., 3rd Rev. Ed. New York: John Wiley and Sons, 1982. 9. Wagner, W.L., Rom, W.A., Merchant, J.A., eds. Health Issues Related to Metal and Nonmetallic Mining. Boston: Butterworth Publishers, 1983.
- 26. Wolf, A.F. Occupational Disease of the Lungs. Part I. Ann. Allergy 35:1-6, 1975.
- 27. Wolf, A.F. Occupational Diseases of the Lungs. Part II. Inhalation diseases due to inorganic dust. Ann. Allergy. 35:87-92, 1975.

- 28. Wolf, A.F. Occupational Diseases of the Lungs. Part III. Pulmonary disease due to inhalation of noxious gases, aerosols, or fumes. Ann. Allergy. 35:165-171, 1975.
 - III. Pulmonary Bioassays
- 29. Henderson, R.F., E.G. Damon, and T.R. Henderson. Early damage indicators in the lungs: Lactate dehydrogenase activity in the airways. *Toxicol. Appl. Pharmacol.* 44:291-297, 1978.
- 30. Kavet, R.I., and Brain, J.D. Methods to quantify endocytosis: a review. J. Reticuloendothel. Soc. 27:201-221, 1980.
- 31. Beck, E.D., Brain, J.D., and Bohannon, D.E. An in vivo hamster bioassay to assess the toxicity of particulates for the lungs. *Toxicol. Appl. Phannacol.* 66:9-29, 1982.
- 32. Smith, T.J., Beck, B.D., Brain, J.D., Hinds, W.C., Baron, S.G., and Weil, L. Prediction of pneumoconiosis risk by bioassays of particulates from occupational exposures. In: *Inhaled Particles, V.*, Walton, W.H. ed., Oxford: Pergamon Press, pp. 163-176, 1982. Also in *Ann. Occup. Hyg.* 86:163-176, 1982.
- 33. Beck, B.D., Gerson, B., Feldman, H.A., and Brain, J.D. Lactic dehydrogenase isoenzymes in hamster lung lavage fluid after lung injury. *Toxicol. Appl. Pharmacol.* 71:59-71, 1983.
- 34. Henderson, R.F. The use of bronchoalveolar lavage to detect lung damage. Environ. Health Perspect. 56: 115-129, 1984.
- 35. Brain, J.D., and Beck, B.D. Bronchoalveolar lavage. In: Toxicology of Inhaled Materials, Handbook of Experimental Pharmacology, Vol. 75, Witchi, H. and Brain, J.D., eds. Berlin: Springer Verlag, pp. 203-226, 1985.
- 36. Brain, J.D. and B.D. Beck. Bioassays for mineral dusts and other particulates. In: In Vitro Effects of Mineral Dusts., Beck, E.G. and Bignon, J., eds. NATO ASI Series Vol. G3. Berlin: Springer Verlag, pp. 323-335, 1985.
- 37. Henderson, R.F., J.M. Benson, F.F. Hahn, C.H. Hobbs, R.K. Jones, J.L. Mauderly, R.O. McClellan, and J.A.Pickrell. New approaches for the evaluation of pulmonary toxicity: Bronchoalveolar lavage fluid analysis. Fund. Appl. Toxicol. 5: 451-458, 1985.
- 38. Beck, B.D., E.J. Clabrese, and P.D. Anderson. The use of toxicology in the regulatory process. *Principles and Methods of Toxicology, 2nd Edition.* (A.W. Hayes, Editor), Raven Press Ltd., New York, pp. 1-28, 1989.



Thursday, September 5

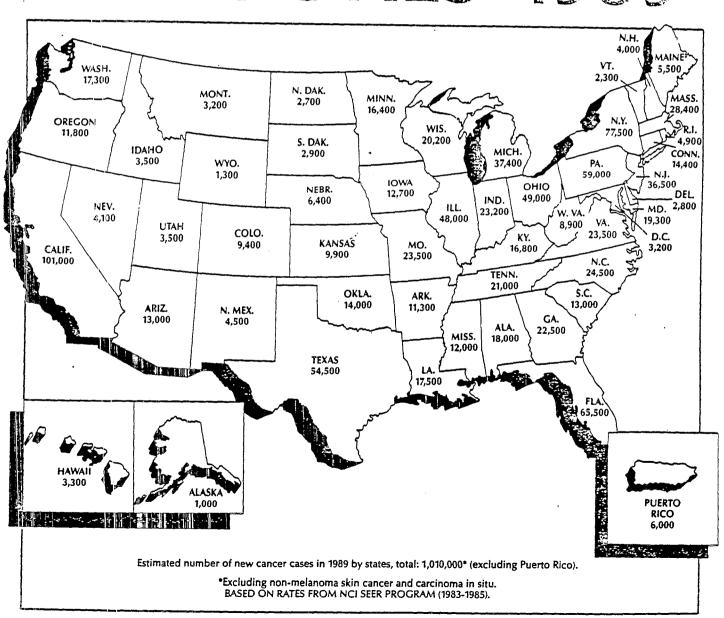
| | Cancer & Cancer Modeling | |
|---------------|--|---------|
| 8:30 - 9:30 | What is Cancer? | Upton |
| 9:30 - 9:45 | Refreshment Break | |
| 9:45 - 11:15 | Cancer Modeling | Cohen |
| 11:15 - 11:30 | Break | |
| | Applications of Expert Judgment | |
| 11:30 - 12:15 | Applications of Expert Judgment in Risk Analysis | Moeller |
| 12:15- 1:15 | Lunch | |
| | Exposure Assessment | |
| 1:15 - 2:45 | The Respiratory System as an Entry for Exposure | Valberg |
| 2:45 - 3:15 | Refreshment Break | |
| 3:15 - 4:45 | Assessment of Exposures | Ryan |

What is Cancer?

 \mathbf{Upton}



CANCER FACTS & FOURES 1989



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*Table/Chart

SOURCES OF STATISTICS

Incidence

Since there is no national office which records every new cancer case, there is no way of knowing exactly how many new cases of cancer are diagnosed each year. In the past, estimates of cancer incidence were made by extrapolating from the experience of the few population-based cancer registries.

Estimates of incidence in Facts & Figures editions prior to 1974 were based on data from two state cancer registries. The issues from 1974 through 1978 used information from the National Cancer Institute's Third National Cancer Survey (1969-1971) of nine major areas of the United States.

Then in 1973, NCI began a new and larger program, gathering data from 11 population-based registries. It is called SEER, standing for Surveillance, Epidemiology and End Results. Beginning with the 1979 edition of Facts & Figures, SEER incidence information has been used. Each time a new data base is introduced, there may be some sharp changes in figures, due to the more accurate data. The changes do NOT indicate either a cancer epidemic or miracle cure.

For valid comparisons between years, incidence statistics from the 1974 through 1978 editions of Facts & Figures may be compared

with one another, while those from the 1979 to 1984 editions may be compared.

The latest available information for this 1989 edition is SEER data from the years 1983-1985.

Mortality

The source for mortality statistics has remained constant over the years: the National Center for Health Statistics, Department of Health and Human Services.

The 1989 figures are estimates based on the latest available information, which includes mortality data through 1985.

Beginning with the 1981 edition of Facts & Figures, mortality rates per 100,000 population were age-adjusted to the 1970 census population, rather than the 1940 census population. Comparing these charts and figures with those of previous years may indicate false trends.

Survival

Because of the 5-year waiting period, survival statistics take longer to compile. In this edition, we show the latest survival rates for cases diagnosed in the period 1979-84 in the SEER program.

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CANCER: BASIC DATA

BASIC DATA

What is cancer?

Cancer is a large group of diseases characterized by uncontrolled growth and spread of abnormal cells. If the spread is not controlled or checked, it results in death. However, many cancers can be cured if detected and treated promptly.

How is cancer treated?

By surgery, radiation, radioactive substances, chemicals, hormones and immunotherapy.

Who gets cancer?

Cancer strikes at any age. It kills more children 3 to 14 than any other disease. And cancer strikes more frequently with advancing age. In the 1980's, there were estimated over 4.5 million cancer deaths, almost 9 million new cancer cases, and some 15 million people under medical care for cancer.

How many people alive today will get cancer?

About 76 million Americans now living will eventually have cancer; about 30%, according to present rates. Over the years, cancer will strike in approximately three out of four families.

How many people alive today have ever had cancer?

There are over 5 million Americans alive today who have a history of cancer, 3 million of them with diagnosis five or more years ago. Most of these 3 million can be considered cured, while others still have evidence of cancer. By "cured" is meant that a patient has no evidence of disease and has the same life expectancy as a person who never had cancer.

The decision as to when a patient may be considered cured is one that must be made by the physician after examining the individual patient. For most forms of cancer, five years without symptoms following treatment is the accepted time. However, some patients can be considered cured after one year, others after three years, whereas some have to be followed much longer than five years.

How many new cases will there be this year?

In 1989 about 1,010,000 people will be diagnosed as having cancer.*

How many people are surviving cancer?

In the early 1900's few cancer patients had any hope of long-term survival. In the 1930's less than one in five was alive at least five years after treatment. In the 1940's it was one in four, and in the 1960's it was one in three.

Today, about 405,000 Americans, or 4 out of 10 patients who get cancer this year, will be alive 5 years after diagnosis. The gain from 1 in 3 to 4 in 10 represents about 67,000 persons this year. This 4 in 10, or about 40% is called the "observed" survival rate. When normal life expectancy is taken into consideration (factors such as dying of heart disease, accidents and diseases of old age) 49% will be alive 5 years after diagnosis. This is the "relative" survival rate, and is considered a more accurate yardstick of our battle against cancer.

Could more people be saved?

Yes. About 178,000 people with cancer will probably die in 1989 who might have been saved by earlier diagnosis and prompt treatment.

How many people will die?

This year about 502,000 will die of the disease—1,375 people a day, about one every 63 seconds. Of every five deaths from all causes in the U.S., one is from cancer. In 1988 an estimated 494,000 Americans died of cancer. In 1987 it was 483,000; in 1986 the figure was 469,376.

What is the national death rate?

There has been a steady rise in the age-adjusted** national death rate. In 1930 the number of cancer deaths per 100,000 population was 143. In 1940 it was 152. By 1950 it had risen to 158 and in 1986 the number was 171. The major cause of these increases has been cancer of the lung. Except for that form of cancer, age-adjusted cancer death rates for major sites are leveling off, and in some cases declining.

Can cancer be prevented?

Some cancers, not all. Most lung cancers are caused by cigarette smoking, and most skin cancers by frequent overexposure to direct sunlight. These cancers can be prevented by avoiding their causes. Certain cancers caused by occupational-environmental factors can be prevented by eliminating or reducing contact with carcinogenic agents. See Prevention section, pp. 18-22.

^{*}These estimates of the incidence of cancer are based upon data from the National Cancer Institute's SEER Program (1983-1985). Non-melanoma skin cancer and carcinoma in situ have not been included in the statistics. The incidence of non-melanoma skin cancer is estimated to be over 500,000 cases annually.

^{**}Age-adjusted—a method used to make valid statistical comparisons by assuming the same age distribution among different groups being compared.

BASIC DATA

HOW CANCER WORKS

Normally, the cells that make up the body reproduce themselves in an orderly manner so that worn-out tissues are replaced, injuries are repaired and growth of the body proceeds.

Occasionally, certain cells undergo an abnormal change and begin a process of uncontrolled growth and spread: One cell divides into two, those redivide into four, and so on. These cells may grow into masses of tissue called tumors—some benign and others malignant (cancerous).

The danger of cancer is that it invades and destroys normal tissue. In the beginning, cancer cells usually remain at their original site, and the cancer is said to be localized. Later, some cancer cells may invade neighboring organs or tissue. This occurs either by direct extension of growth or by becoming detached and carried through the lymph or blood systems to other parts of the body. This is called metastasis of a cancer.

This spread may be regional—confined to one region of the body—when cells are trapped by lymph nodes. If left untreated, however, the cancer is likely to spread throughout the body. That condition is known as advanced cancer, and usually results in death.

Because a case of cancer becomes progressively more serious with each stage, it is important to detect cancer as early as possible. Aids to early detection include cancer's Seven Warning Signals and the cancer risk factors.

TRENDS IN DIAGNOSIS AND TREATMENT

The diagnosis and treatment of cancer has become increasingly individualized. Early detection is followed by more precise staging, and the use of more than one kind of therapy, often in combination.

Some cancers, which only a few decades ago had a very poor outlook, are often being cured today; acute lymphocytic leukemia in children, Hodgkin's disease, Burkitt's lymphoma, Ewing's sarcoma (a form of bone cancer), Wilms' tumor (a kidney cancer in children), rhabdomyosarcoma (a cancer in certain muscle tissue), choriocarcinoma (placental cancer), testicular cancer, ovarian cancer and osteogenic sarcoma. Other cancers have not yet yielded to effective treatment, and are the focus of continuing research.

An outstanding example of progress is the improvement in the management of testicular cancer in young men. More precise diagnostic tools and staging allow better selection of treatment. The use of combinations of cancer drugs has resulted in remarkably improved survival. In 20 years, the 5-year survival rate of testicular cancer rose from 63% to 91%.

The following developments indicate the directions of current and future research:

- New ways have been found to use an old drug, 5fluorouracil, more effectively against metastatic colon cancer. By combining it with leukovorin it is a much more potent inhibitor of colon cancer cells.
- Analysis of oncogene products is a promising new means of preclicting which tumors are likely to recur after surgery.
- Use of potent growth factors stimulates normal bone marrow cells to withstand very high doses of chemotherapeutic drugs.
- A genetic fusing of cancer cells with normal cells can produce disease-fighting "monoclonal antibodies" specific antibodies tailored to seek out chosen targets on cancer cells. Their potential in the diagnosis and treatment of cancer is under study.
- New understanding of the causes of pain in cancer patients has increased the options for control. Regular use of oral pain medicines, infusions or injections

- of analgesics, procedures to interrupt pain pathways, are among the effective approaches available.
- Studies with agents like synthetic retinoids (cousins of vitamin A), and other substances are being undertaken to see if recurrences of certain cancers can be prevented. Another step is to see if these agents can reduce cancer in high risk groups.
- New approaches to drug therapy use combination chemotherapy and chemotherapy with surgery or radiation. New classes of agents are being tested for their effectiveness in treating patients resistant to drug therapies now in use.
- Many patients with primary bone cancer now are treated successfully by removing and replacing a section of bone rather than by amputating the leg or arm. Drugs and radiation therapy are being used effectively after bone cancer surgery, resulting in dramatic improvement in survival.
- New high technology diagnostic imaging techniques have replaced exploratory surgery for some cancer patients. Magnetic Resonance Imaging (MRI) is one example of such technology under study. It uses a huge electromagnet to detect tumors by sensing the vibrations of the different atoms in the body. Computerized tomography (CT scanning) uses X rays to examine the brain and other parts of the body. Cross-section pictures are constructed which show a tumor's shape and location more accurately than is possible with conventional x-ray techniques. For patients undergoing radiation therapy, CT scanning may enable the therapist to pinpoint the tumor more precisely to provide more accurate radiation dosage while sparing normal tissue.
- Immunotherapy holds the hope of enhancing the body's own disease-fighting systems to control cancer. Interferon, interleukin-2 and other biologic response modifiers are under study. Recently, interferon was made available as the treatment for hairy cell leukemia, a rare blood cancer of older Americans. Interleukin-2 is under very active research in the treatment of kidney cancer and melanoma.

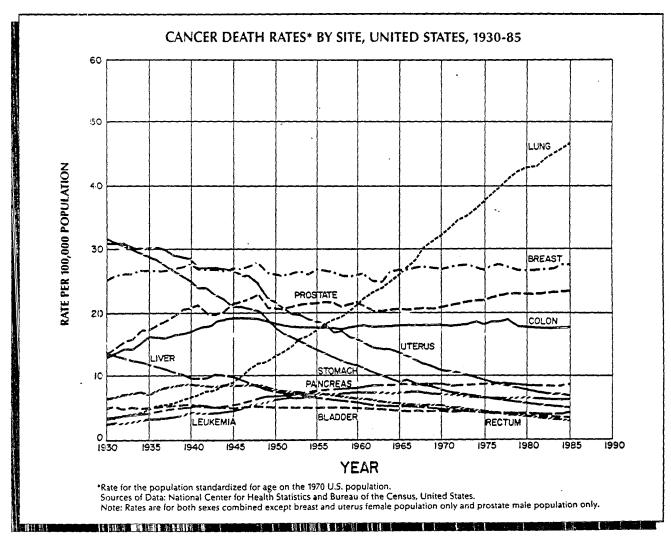
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BASIC DATA

This research area will take many years to find the proper role of these agents in cancer treatment.

- Many cancers are caused by a two-stage process through exposure to substances known as initiators and promoters. Research scientists are exploring ways of interrupting these processes to prevent the development of cancer.
- New technologies have made it possible to use bone marrow transplantation as an important treatment option in selected patients with aplastic anemia and leukemia. Bone marrow transplantation for other cancers is under study. The administration of larger doses of anti-cancer drugs or radiation therapy may be tolerated by some patients if their bone marrow is stored and later transplanted to restore marrow function (autologous bone marrow transplants).
- Hyperthermia is a way to increase the heat or temperature of the entire body or a part of the body. It is known that heat can kill cancer cells. A cell temperature of 45 degrees kills cancer cells. A temperature of 42-43 degrees makes the cell more susceptible to damage by ionizing radiation (X rays). Studies are underway to learn if hyperthermia can increase the effect of radiation or chemotherapy.

- With medical progress producing longer survival periods for many cancer patients, clinical concerns are expanding to include not only patients' physical well-being but also their psychosocial needs. The patient's and family's reactions to the disease, sexual concerns, employment and insurance needs, and ways to provide psychosocial support, have emerged as important areas of research and clinical care.
- Improvements in cancer treatment have made possible more conservative management of some early cancers. In early cancer of the larynx, many patients have been able to retain their larynx and their voice; in colorectal cancer, fewer permanent colostomies are needed; and the surgery required in many cases of breast cancer is often more limited.
- Prostatic ultrasound, a rectal probe using ultrasonic waves producing an image of the prostate, is currently being investigated as a potential means to increase the early detection of occult, or not clinically suspected, prostate cancer.
- Neoadjuvant chemotherapy has been successful against certain types of cancers. This involves giving chemotherapy to shrink the cancer and then removing it surgically.



NEW CANCER CASES—1989 Estimated New Cancer Cases for All Sites Plus Major Sites, by State—1989

| | ALL SITES* | SITES* MAJOR SITES | | | | | | | | | | |
|--------------------------------|-----------------|--------------------|-------------------|--------------|--------------|--------------|--------------|------------------|--------------|--------------|--|--|
| | Number | | | | | | | | | | | |
| STATE | of Cases | Female Breast | Colon & Rectum | Lung | Oral | Uterus | Prostate | Skin Melanoma | Pancreas | Leukemia | | |
| Alabama | 18,000 | 2,400 | 2,300 | 2,800 | 450 | 950 | 2,100 | 400 | 500 | 450 | | |
| Alaska | 1,000 | 150 | 125 | 150 | 40 | 20 | 100 | 50 | 20 | 10 | | |
| Arizona | 13,000 | 1,800 | 1,700 | 1,900 | 350 | 550 | 1,500 | 300 | 350 | 375 | | |
| Arkansas | 11,300 | 1,100 | 1,500 | 1,900 | 200 | 400 | 1,000 | 350 | 350 | 300 | | |
| California | 101,000 | 14,200 | 13,500 | 15,400 | 3,500 | 5,000 | 10,000 | 3,200 | 2,600 | 2,800 | | |
| Colorado | 9,400 | 1,500 | 1,500 | 1,200 | 225 | 450 | 1,100 | 400 | 250 | 250 | | |
| Connecticut | 14,400 | 2,200 | 2,300 | 2,000 | 450 | 600 | 1,400 | 400 | 375 | 375 | | |
| Delaware | 2,800 | 400 | 450 | 500 | 40 | 125 | 275 | 70 | 70 | 80 | | |
| Dist. of Columbia | 3,200 | 450 | 400 | 450 | 250 | 150 | 450 | 60 | 90 | 60 | | |
| Florida | 65,500 | 8,300 | 10,200 | 10,600 | 2,200 | 2,800 | 7,600 | 1,800 | 1,700 | 1,600 | | |
| Georgia | 22,500 | 2,800 | 2,900 | 3,700 | 850 | 1,100 | 2,400 | 600 | 550 | 600 | | |
| Hawaii | 3,300 | 350 | 450 | 450 | 150 | 150 | 275 | 80 | 90 | 80 | | |
| Idaho | 3,500 | 500 | 475 | 475 | 60 | 125 | 425 | 150 | 80 | 125 | | |
| Illinois | 48,000 | -7,000 | 7,800 | 7,400 | 1,400 | 2,400 | 4,700 | 950 | 1,300 | 1,300 | | |
| Indiana | 23,200 | 3,200 | 3,700 | 3,800 | 650 | 1,200 | 2,200 | 600 | 550 | 550 | | |
| lowa | 12,700 | 1,800 | 2,100 | 1,800 | 400 | 550 | 1,500 | 300 | 375 | 375 | | |
| Kansas | 9,900 | 1,400 | 1,600 | 1,600 | 300 | 450 | 1,200 | 200 | 300 | 325 | | |
| Kentucky | 16,800 | 2,100 | 2,500 | 3,000 | 450 | 850 | 1,600 | 350 | 375 | 425 | | |
| Louisiana | 17,500 | 2,200 | 2,200 | 3,000 | 550 | 750 | 1,700 | 300 | 500 | 400 | | |
| Maine | 5,500 | 750 | 950 | 850 | 150 | 250 | 600 | 100 | 150 | 150 | | |
| Maryland | 19,300 | 2,700 | 2,900 | 3,000 | 650 | 800 | 1,900 | 550 | 400 | 450 | | |
| Massachusetts | 28,400 | 4,800 | 4,500 | 3,800 | 800 | 1,000 | 2,600 | 800 | 700 | 700 | | |
| Michigan | 37,400 | 5,500 | 5,300 | 5,800 | 1,000 | 1,700 | 3,600 | 900 | 950 | 1,000 | | |
| Minnesota | 16,400 | 2,300 | 2,600 | 2,100 | 400 | 650 | 2,000 | 400 | 450 | 450 | | |
| Mississippi | 12,000 | 1,100 | 1,400 | 1,800 | 300 | 600 | 1,200 | 250 | 325 | 300 | | |
| Missouri | 23,500 | 3,200 | 3,900 | 3,700 | 700 | 1,200 | 2,000 | 600 | 650 | 700 | | |
| Montana | 3,200 | 500 | 425 | 425 | 60 | 150 | 400 | 90 | 100 | 100 | | |
| Nebraska | 6,400 | 900 | 1,100 | 900 | 150 | 350 | 750 | 175 | 225 | 175 | | |
| Nevada | 4,100 | 500 | 500 | 750 | 150 | 175 | 375 | 150 | 90 | 70 | | |
| New Hampshire | 4,000 | 650 | 650 | 600 | 80 | 200 | 400 | 125 | 125 | 90 | | |
| New Jersey | 36,500 | 5,500 | 6,200 | 5,300 | 1,200 | 1,800 | 3,500 | 950 | 1,000 | 850 | | |
| New Mexico | 4,500 | 600 | 600 | 550 | 125 | 175 | 550 | 80 | 150 | 150 | | |
| New York | 77,500 | 12,100 | 13,200 | 10,900 | 2,500 | 4,000 | 7,900 | 2,100 | 2,300 | 2,000 | | |
| North Carolina | 24,500 | 3,400 | 3,200 | 4,000 | 900 | 1,300 | 2,700 | 750 | 700 | 700 | | |
| North Dakota | 2,700 | 400 | 450 | 325 | 70 | 125 | 450 | 40 | 90 | 90 | | |
| Ohio | 49,000 | 6,800 | 7,700 | 7,900 | 1,400 | -2,200 | 4,700 | 1,200 | 1,300 | 1,300 | | |
| Okiahoma | 14,000 | 1,800 | 1,900 | 2,500 | 400 | 550 | 1,400 | 500 | 425 | 450 | | |
| Oregon | 11,800 | 1,700 | 1,600 | 2,000 | 300 | 425 | 1,200 | 350 | 325 | 350 | | |
| Pennsylvania Rhode Island | 59,000 4,900 | 8,800 700 | 10,000 900 | 8,600 700 | 1,700 200 | 2,500 200 | 5,300 500 | 1,600 150 | 1,500 150 | 1,500 100 | | |
| | - | | | | | | | 400 | 350 | 250 | | |
| South Carolina South Dakota | 13,000 2,900 | 1,900 425 | 1,700 500 | 2,000 375 | 500 40 | 750 125 | 1,500 350 | 80 | 90 | 100 | | |
| Tennessee | 21,000 | 2,600 | 2,800 | 3,500 | 700 | 950 | 2,200 | 500 | 550 | 600 | | |
| Texas | 54,500 | 7,300 | 7,200 | 8,800 | 1,800 | 2,600 | 5,000 | 1,600 | 1,400 | 1,700 | | |
| Utah | 3,500 | 550 | 450 | 350 | 100 | 200 | 600 | 100 | 100 | 125 | | |
| Vermont | 2,300 | 350 | 375 | 350 | 80 | 150 | 250 | 50 | 50 | 90 | | |
| Virginia | 23,500 | 3,300 | 3,400 | 3,800 | 800 | 1,100 | 2,500 | 700 | 600 | 600 | | |
| Washington | 17,300 | 2,500 | 2,300 | 2,800 | 550 | 850 | 1,800 | 500 | 500 | 450 | | |
| West Virginia | 8,900 | 1,200 | 1,200 | 1,500 | 200 | 375 | 800 | 200 | 250 | 250 | | |
| Wisconsin | 20,200 | 3,100 | 3,200 | 2,700 | 450 | 900 | 2,300 | 400 | 550 | 650 | | |
| Wyoming | 1,300 | 225 | 200 | 200 | 30 | 30 | 150 | 50 | 30 | 30 | | |
| | | | | | 24 000 | 47.000 | 103.000 | 27.000 | 27.000 | 27.000 | | |
| United States | 1,010,000 | 142,000 | 151,000 | 155,000 | 31,000 | 47,000 | 103,000 | 27,000 | 27,000 | 27,000 | | |
| Puerto Rico | 6,000 | 450 | 450 | 350 | 425 | 750 | 400 | 500 | 100 | 175 | | |

^{*}Does not include carcinoma in situ or non-melanoma skin cancer.

These estimates are offered as a rough guide and should not be regarded as definitive. They are calculated according to the distribution of estimated 1989 cancer deaths by state. Especially note that year-to-year changes may only represent improvements in the basic data.

CANCER DEATHS—1989
Estimated Cancer Deaths for All Sites Plus Major Sites, by State—1989

| | AL | L SITES | MAJOR SITES | | | | | | | | |
|-------------------------|-----------------|----------------------------|------------------|-------------------|----------------|------------|------------|--------------|---------------|------------|--------------|
| | Number | Death Rate | _ | | | | | | Skin | | |
| STATE | of Deaths | per 100,000 Population* | Female Breast | Colon & Rectum | Lung | Oral | Uterus | Prostate | Mela- noma | Pancreas | Leukemia |
| Alabama | 8,900 | 214 | 700 | 950 | 2,600 | 125 | 200 | 550 | 100 | 425 | 300 |
| Alaska | 500 | 221 | 30 | 50 | 150 | 10 | 10 | 20 | 10 | 25 | 10 |
| Arizona | 6,500 | 180 | 550 | 700 | 1,800 | 100 | 50 | 400 | 70 | 300 | 225 |
| Arkansas | 5,600 | 190 | 350 | 600 | 1,800 | 60 | 100 | 300 | 80 | 300 | 225 |
| California | 50,000 | 181 | 4,400 | 5,500 | 14,100 | 950 | 900 | 2,800 | 700 | 2,500 | 1,800 |
| Colorado | 4,700 | 141 | 450 | 600 | 1,200 1,800 | 60 | 70 125 | 275 375 | 80 90 | 250 400 | 200 275 |
| Connecticut Delaware | 7,200 1,400 | 217 250 | 650 125 | 950 175 | 450 | 125 10 | 20 | 3/3 60 | 10 | 60 | 2/3 50 |
| Dist. of Columbia | 1,400 | 250 264 | 175 | 175 | 400 | 70 | 60 | 125 | 10 | 100 | 50 50 |
| Florida | 32,500 | 182 | 2,500 | 4,100 | 9,800 | 600 | 400 | 2,100 | 400 | 1,600 | 1,000 |
| Georgia | 11,200 | 202 | 850 | 1,200 | 3,400 | 250 | 250 | 700 | 150 | 500 | 400 |
| Hawaii | 1,700 | 191 | 100 | 175 | 375 | 50 | 20 | 80 | 20 | 80 | 50 |
| Idaĥo | 1,800 | 158 | 150 | 175 | 400 | 20 | 25 | 125 | 30 | 100 | 80 |
| Illinois | 24,000 | 201 | 2,100 | 3,100 | 6,600 | 450 | 600 | 1,300 | 200 | 1,300 | 900 |
| Indiana | 11,500 | 217 | 950 | 1,500 | 3,500 | 175 | 300 | 600 | 125 | 550 | 425 |
| lowa | 6,400 | 190 | 550 | 850 | 1,600 | 125 | 125 | 400 | 70 | 350 | 300 |
| Kansas | 4,900 | 171 | 425 | 650 | 1,300 | 90 | 100 | 350 | 50 80 | 275 375 | 225 300 |
| Kentucky | 8,400 | 207 212 | 650 650 | 1,000 900 | 2,800 2,800 | 125 150 | 175 175 | 425 475 | 80 | 450 | 300 |
| Louisiana Maine | 8,800 2,800 | 199 | 225 | 400 | 800 | 40 | 60 | 175 | 20 | 150 | 90 |
| Maryland | 9,600 | 244 | 800 | 1,200 | 2,700 | 175 | 175 | 500 | 125 | 425 | 300 |
| Massachusetts | 14,100 | 220 | 1,500 | 1,900 | 3,500 | 250 | 275 | 750 | 175 | 650 | 475 |
| Michigan | 18,600 | 226 | 1,600 | 2,100 | 5,300 | 275 | 400 | 1,000 | 200 | 900 | 650 |
| Minnesota | 8,100 | 181 | 700 | 1,100 | 2,000 | 125 | 125 | 550 | 90 | 450 | 350 |
| Mississippi | 5,100 | 186 | 325 | . 500 | 1,700 | 80 | 100 | 350 | 60 | 300 | 225 |
| Missouri | 11,800 | 196 | 950 | 1,500 | 3,400 | 175 | 250 | 550 100 | 125 20 | 550 100 | 450 70 |
| Montaria | 1,600 | 186 | 150 300 | 175 450 | 375 800 | 20 40 | 30 70 | 200 | 40 | 200 | 175 |
| Nebraska Nevada | 3,300 2,100 | 173 216 | 150 | 200 | 600 | 40 | 20 | 100 | 30 | 80 | 40 |
| New Hampshire | 2,100 | 197 | 200 | 250 | 550 | 30 | 40 | 90 | 30 | 100 | 70 |
| New Jersey | 18,100 | 230 | 1,600 | 2,500 | 4,900 | 325 | 375 | 950 | 225 | 900 | 550 |
| New Mexico | 2,300 | 168 | 200 | 250 | 500 | 30 | 40 | 150 | 20 | 125 | 70 |
| New York | 38,500 | 200 | 3,800 | 5,400 | 9,800 | 750 | 950 | 2,200 | 475 | 2,100 | 1,400 |
| North Carolina | 12,200 | 203 | 1,000 | 1,300 | 3,700 | 225 | 275 | 750 | 175 | 550 | 425 |
| North Dakota | 1,300 | 171 | 125 | 175 | 300 | 20 | 20 | 125 | 10 | 90 | 60 |
| Ohio | 24,000 | 227 | 2,100 | 3,100 | 7,300 | 400 | 600 100 | 1,300 | 250 100 | 1,200 | 850 275 |
| Oklahoma | 7,000 5,900 | 163 198 | 550 500 | 800 650 | 2,300 1,800 | 100 100 | 75 | 350 | 70 | 300 | 225 |
| Oregon Pennsylvania | 29,500 | 221 | 2,600 | 4,000 | 7,800 | 475 | 700 | 1,500 | 350 | 1,400 | 1,000 |
| Rhode Island | 2,500 | 227 | 250 | 350 | 650 | 60 | 40 | 125 | 30 | 125 | . 70 |
| South Carolina | 6,500 | 209 | 550 | 650 | 1,900 | 125 | 125 | 425 | 90 | 325 | 175 |
| South Dakota | 1,500 | 180 | 125 | 200 | 325 | 10 | 30 | 125 | 20 | 100 | 80 |
| Tennessee | 10,400 | 202 | 800 | 1,100 | 3,300 | 200 | 200 | 600 | 125 | 500 | 375 1,000 |
| Texas | 27,000 | 155 | 2,200 | 2,900 | 8,100 275 | 475 20 | 500 | 1,400 175 | 350 | 1,300 | 80 |
| Utah | 1,800 | 118 | 175 100 | 175 150 | 275 | 20 | 30 | 70 | 10 | 60 | 50 |
| Vermont Virginia | 1,200 11,700 | 196 219 | 950 | 1,400 | 3,500 | 225 | 225 | 650 | 150 | 500 | 375 |
| Washington | 8,600 | 181 | 750 | 900 | 2,600 | 150 | 150 | 500 | 100 | 425 | 300 |
| West Virginia | 4,400 | 202 | 350 | 500 | 1,400 | 60 | 100 | 225 | 50 | 200 | 175 |
| Wisconsin | 10,000 | 1 | 950 | 1,300 | 2,500 | 125 | 175 | 650 | 90 | 500 | 425 |
| Wyoming | 700 | 3 | 70 | 75 | 175 | 10 | 10 | 30 | 10 | 40 | 30 |
| United States | 502,000 | | 43,000 | 61,000 | 142,000 | 8,700 | 10,000 | 28,500 | 6,000 | 25,000 | 18,000 |
| Puerto Rico | 3,500 | 150 | 200 | 250 | 400 | 175 | 150 | 300 | 400 | 80 | 150 |

^{*}Adjusted to the age distribution of the 1970 U.S. Census Population.

ESTIMATED NEW CANCER CASES AND DEATHS BY SEX FOR ALL SITES—1989*

| | ESTIMATED NEW CASES | | | ESTIMATED DEATHS | | | | |
|-------------------------------------|---------------------|----------------|------------|------------------|----------------|----------------|--|--|
| | Total | Male | Female | Total | Male | Female | | |
| ALL SITES | 1,010,000* | 505,000* | 505,000* | 502,000 | 266,000 | 236,000 | | |
| Buccal Cavity & Pharynx (ORAL) | 30,600 | 20,600 | 10,000 | 8,650 | 5,775 | 2,875 | | |
| Lip | 4,200 | 3 <i>,</i> 700 | 500 | 100 | 75 | 25 | | |
| Tongue | 6,000 | 3,900 | 2,100 | 1,950 | 1,300 | 650 | | |
| Mouth | 11,700 | 7,000 | 4,700 | 2,600 | 1,600 | 1,000 | | |
| Pharynx | 8,700 | 6,000 | 2,700 | 4,000 | 2,800 | 1,200 | | |
| Digestive Organs | 227,800 | 115,200 | 112,600 | 123,000 | 64,400 | 58,600 | | |
| Esophagus | 10,100 | 7,200 | 2,900 | 9,400 | 6,900 | 2,500 | | |
| Stomach | 20,000 | 11,900 | 8,100 | 13,900 | 8,200 | 5,700 | | |
| Small Intestine | 2,700 | 1,400 | 1,300 | 900 | 500 | 400 | | |
| Large Intestine (COLON-RECTUM) | 107,000 | 50,000 | 57,000 | 53,500 | 26,000 | 27,500 | | |
| Kectum) | 44,000 | 23,000 | 21,000 | 7,800 | 4,000 | 3,800 | | |
| Liver & Biliary Passages | 14,500 | 7,500 | 7,000 | 11,400 | 5,800 | 5,600 | | |
| Pancreas | 27,000 | 13,000 | 14,000 | 25,000 | 12,500 | 12,500 | | |
| Other & Unspecified Digestive | 2,500 | 1,200 | 1,300 | 1,100 | 500 | 600 | | |
| Respiratory System | 171,600 | 114,000 | 57,600 | 147,100 | 96,900 | 50,200 | | |
| Larynx | 12,300 | 10,000 | 2,300 | 3,700 | 3,000 | 700 | | |
| LUNG | 155,000 | 101,000 | 54,000 | 142,000 | 93,000 | 49,000 | | |
| Other & Unspecified Respiratory | 4,300 | 3,000 | 1,300 | 1,400 | 900 | 500 | | |
| Bone | 2,100 | 1,200 | 900 | 1,300 | 700 | 600 | | |
| Connective Tissue | 5,600 | 3,000 | 2,600 | 3,000 | 1,400 | 1,600 | | |
| SKIN | 27,000** | 14,500** | 12,500** | 8,200† | 5,200 | 3,000 | | |
| BREAST | 142,900*** | 900*** | 142,000*** | 43,300 | 300 | 43,000 | | |
| Genital Organs | 181,800*** | 109,900 | 71,900*** | 52,200 | 29,100 | 23,100 | | |
| Cervix Uteri } (UTERUS) | 13,000*** | · – | 13,000*** | 6,000 | _ | 6,000 | | |
| Corpus, Endometrium 3 (OTEROS) | 34,000 | _ | 34,000 | 4,000 | _ | 4,000 | | |
| Ovary | 20,000 | - | 20,000 | 12,000 | | 12,000 | | |
| Other & Unspecified Genital, Female | 4,900 | _ | 4,900 | 1,100 | _ | 1,100 | | |
| Prostate | 103,000 | 103,000 | _ | 28,500 | 28,500 | | | |
| Testis | 5,700 | 5,700 | _ | 350 | 350 | _ | | |
| Other & Unspecified Genital, Male | 1,200 | 1,200 | | 250 | 250 | | | |
| Urinary Organs | 70,200 | 49,000 | 21,200 | 20,200 | 12,900 | 7,300 | | |
| Bladder | 47,100 | 34,500 | 12,600 | 10,200 10,000 | 6,900 6,000 | 3,300 4,000 | | |
| Kidney & Other Urinary | 23,100 | 14,500 | 8,600 | | | | | |
| Eye | 1,900 | 1,000 | 900 | 300 | 150 | 150 | | |
| Brain & Central Nervous System | 15,000 | 8,200 | 6,800 | 11,000 | 6,000 | 5,000 | | |
| Endocrine Glands | 12,600 | 3,700 | 8,900 | 1,750 | 775 | 975 | | |
| Thyroid | 11,300 | 3,000 | 8,300 | 1,025 | 375 | 650 | | |
| Other Endocrine | 1,300 | 700 | 600 | 725 | 400 . | 325 | | |
| Leukemia | 27,300 | 15,200 | 12,100 | 18,100 | 9,800 | 8,300 | | |
| Lymphocytic Leukemia | 13,000 | <i>7,</i> 500 | 5,500 | 7,000 | 3,900 | 3,100 | | |
| Granulocytic Leukemia | 13,300 | 7,200 | 6,100 | 10,600 | 5,600 | 5,000 | | |
| Monocytic Leukemia | 1,000 | 500 | 500 | 500 | 300 | 200 | | |
| Other Blood & Lymph Tissues | 51,800 | 27,000 | 24,800 | 27,400 | 14,100 | 13,300 | | |
| Hodgkin's Disease | 7,400 | 4,200 | 3,200 | 1,500 | 900 | 600 | | |
| Non-Hodgkin's Lymphomas | 32,800 | 16,800 | 16,000 | 17,300 | 8,900 | 8,400 | | |
| Multiple Myeloma | 11,600 | 6,000 | 5,600 | 8,600 | 4,300 | 4,300 | | |
| All Other & Unspecified Sites | 41,800 | 21,600 | 20,200 | 36,500 | 18,500 | 18,000 | | |

NOTE: The estimates of new cancer cases are offered as a rough guide and should not be regarded as definitive. Especially note that year-to-year changes may only represent improvements in the basic data. ACS six major sites appear in boldface caps.

†Melanoma 6,000; other skin 2,200

^{*}Carcinoma in situ and non-melanoma skin cancers are not included in totals. Carcinoma in situ of the uterine cervix accounts for more than 50,000 new cases annually, and carcinoma in situ of the female breast accounts for about 10,000 new cases annually. Non-melanoma skin cancer accounts for more than 500,000 new cases annually.

^{**}Melanoma only.

^{***}Invasive cancer only.

LUNG CANCER

Incidence: An estimated 155,000 new cases in 1989. The incidence rate in white males rose from 82.7 per 100,000 in 1982 to 84.2 in 1984. The incidence rate in white females and in black males and females also rose.

Mortality: An estimated 142,000 deaths in 1989. The age-standardized lung cancer death rate for women is higher than that of any other cancer. It has surpassed breast cancer which for over 50 years was the number one cancer killer of women.

Warning Signals: A persistent cough; sputum streaked with blood; chest pain; recurring attacks of pneumonia or bronchitis.

Risk Factors: Cigarette smoking; history of smoking 20 or more years; exposure to certain industrial substances such as asbestos, particularly for those who smoke. Involuntary smoking increases the risk. Exposure to radiation may also contribute to lung cancer.

Early Detection: Lung cancer is very difficult to detect early; symptoms often don't appear until the disease has advanced considerably. If a smoker quits at the time of early precancerous cellular changes, the damaged bronchial lining often returns to normal. If a smoker continues the habit, cells may form abnormal growth patterns that lead to cancer. Diagnosis may be aided by such procedures as the chest X ray, sputum cytology test and fiberoptic bronchoscopy.

Treatment: Treatment depends on the type of, and stage of lung cancer. Surgery, radiation therapy and chemotherapy are all options. For many localized cancers, surgery is usually the treatment of choice. Since the majority of patients with lung cancer have tumor spread, radiation therapy and chemotherapy are often combined with surgery. In small cell cancer of the lung, chemotherapy alone or combined with radiation has largely replaced surgery as the treatment of choice, with a large percentage of patients experiencing remission—in some cases, long-lasting remission.

Survival: Only 13% of lung cancer patients (all stages, whites and blacks) live five or more years after diagnosis. The rate is 33% for cases detected in a localized stage; but only 24% of lung cancers are discovered that early. Rates have improved only slightly over a recent 10-year period.

COLON AND RECTUM CANCER

Incidence: An estimated 151,000 new cases in 1989, including 107,000 of colon cancer and 44,000 of rectum cancer. Their combined incidence is second only to that of lung cancer (excluding common skin cancers).

Mortality: An estimated 61,300 deaths in 1989, second only to lung cancer. This includes 53,500 for colon cancer and 7,800 for rectum cancer.

Warning Signals: Bleeding from the rectum, blood in the stool, change in bowel habits.

Risk Factors: Personal or family history of colon and rectum cancer; personal or family history of polyps in the colon or rectum; inflammatory bowel disease.

Evidence suggests that bowel cancer may be linked to the diet. A diet high in fat and/or low in fiber content may be a significant causative factor.

Early Detection: The ACS recommends three tests as valuable aids in detecting colon and rectum cancer early in people without symptoms.

The digital rectal examination is performed by a physician during an office visit. The ACS recommends one every year after age 40.

The stool blood slide test is a simple method of testing the feces for hidden blood. The specimen is obtained by the patient at home, and returned to the physician's office, a hospital or clinic for examination. The ACS recommends the test every year after 50.

Proctosigmoidoscopy, known as the "procto," is an examination in which a physician inspects the rectum

and lower colon with a hollow lighted tube. As the site of most colorectal cancers appears to be shifting higher in the colon, longer, flexible instruments are being used as well as the rigid scope. The ACS recommends a procto every 3 to 5 years after the age of 50, following two annual normal exams.

If any of these tests reveals possible problems, a physician may recommend more extensive studies, such as colonoscopy and a barium enema. Colonoscopes view the entire colon.

Treatment: Surgery, at times combined with radiation, is the most effective method of treating colorectal cancer. Chemotherapy is being studied to determine its possible role in treating advanced cases.

In cases of colon cancer, a permanent colostomy, the creation of an abdominal opening for the elimination of body wastes, is seldom needed, and is infrequently required for patients with rectal cancer. One report found permanent colostomies necessary for only 15% of patients whose rectal cancers are detected early. For those who do have permanent colostomies, the Society has a special patient assistance program. (See p. 25)

Survival: When colorectal cancer is detected and treated in an early, localized stage, the 5-year survival rate is 87% for colon cancer and 79% for rectal cancer, compared with 40% and 31% respectively, after the cancer has spread to other parts of the body.

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SELECTED CANCER SITES

BREAST CANCER

Incidence: An estimated 142,900 new cases in the United States during 1989. About one out of 10 women will develop breast cancer at some time during her life

Mortality: An estimated 43,300 deaths (43,000 females; 300 males) in 1989, in females, second only to lung cancer, now the foremost site of cancer deaths in women

Warning Signals: Breast changes that persist such as a lump, thickening, swelling, dimpling, skin irritation, distortion, retraction or scaliness of the nipple, nipple discharge, pain or tenderness.

Risk Factors: Over age 50; personal or family history of breast cancer; never had children; first child after age 30.

Early Detection: The American Cancer Society recommends the monthly practice of breast self-examination (BSE) by women 20 years and older as a routine good health habit. Most breast lumps are not cancer, but only a physician can make a diagnosis.

The American Cancer Society and the National Cancer Institute, in their joint Breast Cancer Detection Demonstration program, found that mammography—a low-dose x-ray examination—could find cancers too small to be felt by the most experienced examiner.

Besides its effectiveness in screening women without symptoms, marninography is recognized as a valuable diagnostic technique for women who do have findings suggestive of breast cancer. Once a breast lump is found, mammography can help determine if there are other lesions in the same or opposite breast which are too small to be felt. All suspicious lumps should

be biopsied for a definitive diagnosis—even when the mammogram is described as normal.

The Society recommends a mammogram every year for asymptomatic women age 50 and over, and a baseline mammogram for those 35 to 39. Asymptomatic women 40 to 49 should have mammography every 1-2 years. In addition, a professional physical examination of the breast is recommended every three years for women 20 to 40, and every year for those over 40.

Treatment: Several methods may be used, depending on the individual woman's preferences and medical situation—surgery varying from local removal of the tumor to mastectomy, radiation therapy, chemotherapy or hormone manipulation. Often two or more methods may be used in combination. Patients should discuss with their physicians possible options available concerning the specific management of their breast cancer.

New techniques in recent years have made breast reconstruction possible after mastectomy, and the cosmetic results are good. Reconstruction now has become an important part of treatment and rehabilitation. (See p. 25)

Survival: The 5-year survival rate for localized breast cancer has risen from 78% in the 1940's to 90% today. If the breast cancer is not invasive (in situ), the survival rate approaches 100%. If the cancer has spread, however, the rate is 60%.

Despite an increasing incidence of breast cancer, longer survival has helped to stabilize mortality rates over the last 50 years.

UTERINE CANCER

Incidence: An estimated 47,000 new invasive cases in 1989, including 13,000 cases of cancer of the cervix, and 34,000 cases of cancer of the endometrium or body of the uterus. Invasive cervical cancer incidence has steadily decreased over the years, while cancer in situ has risen in all groups. Cervical cancer is most common today among low socioeconomic groups but all groups are at risk. Endometrial cancer afflicts mostly mature women, and diagnosis usually is made between the ages of 55 and 69.

Mortality: An estimated 6,000 deaths in 1989 from cervical cancer, 4,000 from endometrial cancer. Overall, the death rate from uterine cancer has decreased more than 70% during the last 40 years, due mainly to the Pap test and regular checkups.

Warning Signals: Intermenstrual or postmenopausal bleeding or unusual discharge.

Risk Factors: For cervical cancer: early age at first intercourse, multiple sex partners. For endometrial cancer: history of infertility, failure of ovulation, prolonged estrogen therapy and obesity.

Early Detection: The Pap test, an examination under a microscope of cells from the cervix and body of the uterus, is a simple procedure which can be performed at appropriate intervals by physicians as part of every pelvic examination. For cervical cancer, women who are or have been sexually active, or have reached age 18 years, should have an annual Pap test and pelvic examination. After a woman has had three or more consecutive satisfactory normal annual examinations, the Pap test may be performed less frequently at the discretion of her physician.

The Pap test is highly effective in detecting early cancer of the uterine cervix; it is only 50% effective in detecting endometrial cancer. Women at high risk of developing endometrial cancer should have an endometrial tissue sample at menopause.

The hormone estrogen frequently is given to women during and after menopause to make up for the decline in estrogens normally produced by the ovaries. Estrogen helps to control menopausal symptoms such as hot flashes or thinning of the vaginal lining causing painful sexual intercourse. For mature women, there are certain risks associated with such treatment, including an increased risk of endometrial cancer. Women and their physicians should carefully discuss

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SELECTED CANCER SITES

the use of postmenopausal estrogens in terms of the benefit and risk to the individual patient.

Treatment: Uterine cancers generally are treated by surgery or radiation, or by a combination of the two. In precancerous (in situ) stages, changes in the cervix may be treated by cryotherapy (the destruction of cells by extreme cold), by electrocoagulation (the destruction of tissue through intense heat by electric current) or by local surgery. Precancerous endometrial changes

may be treated with the hormone progesterone.

Survival: The 5-year survival rate for all cervical cancer patients is 66%. For patients diagnosed early, however, the rate is 80-90%. Cancer in situ is virtually 100%. The figures for endometrial cancer are 83% all stages, 91% early and virtually 100% for endometrial precancerous lesions. During a recent 10-year period, there was moderate improvement for both uterine sites.

OVARIAN CANCER

Incidence: An estimated 20,000 new cases in the United States in 1989. It is estimated that about 1.4% or one out of every 70 newborn girls will develop ovarian cancer during her lifetime. It accounts for 4% of all cancers among women and 27% of the cancers of the female reproductive system.

Mortality: An estimated 12,000 deaths in 1989. Although ovarian cancer ranks second in incidence among gynecological cancers, it causes more deaths than any other cancer of the female reproductive system.

Warning Signals: Ovarian cancer is often "silent," showing no obvious signs or symptoms until late in its development. The most common sign is an enlarged abdomen caused by the collection of fluid. Rarely will there be abnormal vaginal bleeding. In women over 40, vague digestive disturbances (stomach discomfort, gas, distention) which persist and cannot be explained by any other cause may indicate the need for a thorough checkup for ovarian cancer.

Risk Factors: Risk for ovarian cancer increases with age, with highest rates for women 65-84. Women who have never had children are twice as likely to develop ovarian cancer as those who have. A number of interrelated reproductive factors, such as age at first live birth, age at first pregnancy, and number of pregnancies are all involved in varying degrees. In addition, years of ovulation, the product of a number of other interrelated factors such as length of pregnancies and oral contraceptive use (which may themselves actually

decrease risk), are also tied to an observed increased risk. Breast and endometrial cancer increases a woman's chances of developing ovarian cancer twofold. Patients with colorectal cancer are at increased risk of ovarian cancer, although risk decreases over time following diagnosis of their colorectal cancer. Some rare genetic disorders are associated with increased risk. Incidence rates are higher in North America and Northern Europe, and lower in Asia and Africa. Rates are significantly higher for nuns, Jewish women, and women who have never been married.

Early Detection: Periodic, thorough pelvic examinations are important. The Pap test, useful in detecting cervical cancer, does not reveal ovarian cancer. Women over the age of 40 should have a cancer-related checkup every year.

Treatment: Surgery, radiation therapy and drug therapy are all options in the treatment of ovarian cancer. Surgical treatment usually includes the removal of one or both ovaries, the uterus (hysterectomy) and the fallopian tubes. In some very early tumors, only the involved ovary may be removed, especially in young women. In advanced disease, an attempt is made to remove all intra-abdominal disease to enhance the effect of chemotherapy.

Survival: If ovarian cancer is diagnosed and treated early, about 85% of such patients live 5 years or longer. However, when diagnosed in an advanced stage, the survival rate drops to 23%. It has improved with modern chemotherapeutic agents. Overall, the survival rate for ovarian cancer is 38%.

ORAL CANCER

Incidence: An estimated 31,000 new cases in 1989. Incidence is more than twice as high in males as in females, and is most frequent in men over age 40. Cancer can affect any part of the oral cavity, from lip to tongue to mouth and throat.

Mortality: An estimated 8,650 deaths in 1989.

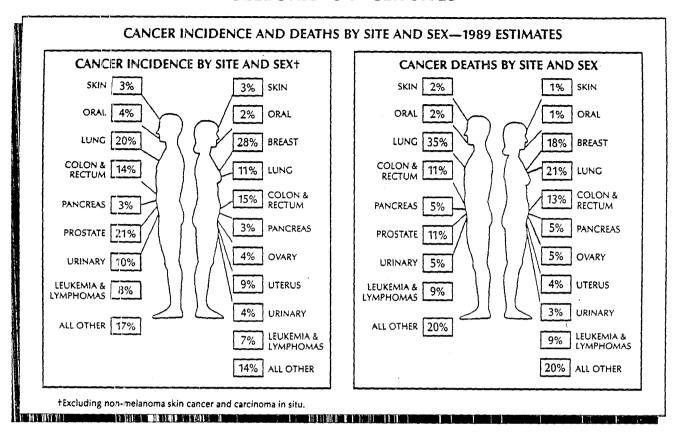
Warning Signals: A sore that bleeds easily and doesn't heal; a lump or thickening; a reddish or whitish patch that persists. Difficulty in chewing, swallowing or moving tongue or jaws are often late changes.

Risk Factors: Cigarette, cigar and pipe smoking; use of smokeless tobacco; excess use of alcohol.

Early Detection: Dentists and primary care physicians have the opportunity, during regular checkups, to see abnormal tissue changes and to detect cancer at an early and curable stage.

Treatment: Principal methods are radiation therapy and surgery. Chemotherapy is being studied as an aid to surgery in advanced disease.

Survival: Five-year survival rates vary substantially depending on the site. Rates range from 32% for cancer of the pharynx to 91% for lip cancer. Overall, 5-year survival for oral cancer patients is about 51%.



PROSTATE CANCER

Incidence: An estimated 103,000 new cases in the United States during 1989. About one out of 11 men will develop prostate cancer at some time during his lifetime. The third highest incidence of cancer in men, next to skin cancer and lung cancer.

Mortality: An estimated 28,500 deaths in 1989, the third leading cause of cancer deaths in men.

Warning Signals: Most signs or symptoms of prostate cancer are nonspecific, and do not distinguish from benign conditions such as infection or prostate enlargement. These include weak or interrupted flow of urine; inability to urinate or difficulty in starting urination; need to urinate frequently, especially at night; blood in the urine; urine flow that is not easily stopped; painful or burning urination; continuing pain in lower back, pelvis or upper thighs.

Risk Factors: Incidence increases with age through the most advanced ages; about 80% of all prostate cancers are diagnosed in men over the age of 65. The disease is more common in northwest Europe and North America; rare in the Near East, Africa, Central and South America. Black Americans have the highest rate of incidence in the world for reasons not currently known. There is some familial association, but it is unclear whether this is due to genetic or environmental association. Dietary fat may be a factor, based on studies conducted internationally. Workers who work with cadmium are found to be at slightly higher risk. Studies of migrating populations have suggested that environmental factors, such as diet and lifestyle, may play an

important role in the risk of developing cancer of the prostate.

Early Detection: Every man over 40 should have a rectal exam as part of his regular annual physical checkup. A new technique, prostate ultrasound is being investigated for the early detection of small non-palpable cancers. This new approach may be of special benefit to high risk men. Men over 40 should be alert to changes such as urinary difficulties, continuing pain in lower back, pelvis or upper thighs, and should see their physician immediately should any occur. The key to saving lives from prostate cancer is early detection and treatment.

Treatment: Surgery, alone or in combination with radiation and/or hormones, and anticancer drugs are all options available in the treatment of prostate cancer. Surgery or radiation therapy may be the treatment chosen to cure prostate cancer if it is found in an early localized state. Hormone treatment and anticancer drugs also may control prostate cancer for long periods by shrinking the size of the tumor and greatly relieving pain.

Survival: Sixty-four percent of all prostate cancers are discovered while still localized within the general region of the prostate; 84% of all patients whose tumors are diagnosed at this stage are alive 5 years after treatment. Survival rates for all stages combined have steadily improved since 1940, and in the last 20 years have increased from 48% to 71%.

BLADDER CANCER

Incidence: An estimated 47,000 new cases of bladder cancer in 1989; 34,500 in males, 12,500 in females. Bladder cancers account for 7% of the new cancer cases diagnosed each year in men and 3% in women. Bladder cancer is the 5th most common form of cancer in males and 10th most common form of cancer in females in this country.

Mortality: An estimated 10,200 deaths in 1989 from bladder cancers, the 8th leading cause of cancer deaths in males and 14th in females.

Warning Signals: Blood in the urine. Usually associated with increased frequency of urination.

Risk Factors: Smoking is the greatest risk factor in bladder cancer, with smokers experiencing twice the risk of nonsmokers. Smoking is estimated to be responsible for about 49% of the bladder cancers among men and 10% among women. Overall, the incidence rate

of bladder cancer is 4 times as great among men as women, and higher in whites than in blacks. People living in urban areas, and dye, rubber and leather workers also are at higher risk. Coffee and artificial sweeteners have been found to increase cancer risk in a few studies but most studies have not found an increased risk.

Diagnosis: Diagnosis of bladder cancer is achieved by examination of the bladder wall with a cystoscope, a slender tube fitted with a lens and light that can be inserted into the tract through the urethra.

Treatment: Surgery, alone or in combination with other treatments, is used in 92% of cases.

Survival: The 5-year survival rate for bladder cancer is 88% when detected in an early stage. For those cancers more advanced, the survival rate drops to 41%.

SKIN CANCER

Incidence: Over 500,000 cases a year, the vast majority of which are highly curable basal or squamous cell cancers. They are more common among individuals with lightly pigmented skin, living at latitudes near the equator. The most serious skin cancer is malignant melanoma, which strikes about 27,000 persons each year. The incidence of melanoma is increasing at the rate of 3.4% per year.

Mortality: An estimated 8,200 deaths this year, 6,000 from malignant melanoma, and 2,200 due to other skin cancers.

Warning Signals: Any unusual skin condition, especially a change in the size or color of a mole or other darkly pigmented growth or spot. Scaliness, oozing, bleeding or the appearance of a bump or nodule, the spread of pigment beyond the border, a change in sensation, itchiness, tenderness or pain are all warning signs of melanoma.

Risk Factors: Excessive exposure to the sun; fair complexion; occupational exposure to coal tar, pitch, creosote, arsenic compounds or radium. Among blacks, because of heavy skin pigmentation, skin cancer is negligible. One study has found that severe sunburn in childhood carries with it an excessive risk of melanoma in later life.

Prevention: Avoid the sun between 10 a.m. and 3 p.m. when ultraviolet rays are strongest, and use protective clothing. Use one of a number of sunscreen preparations, especially those containing such ingredients as PABA (para-aminobenzoic acid). They come in varying strengths, ranging from those that permit gradual tanning to those allowing practically no tanning at all. Children, in particular, should be protected from traumatic sunburns.

Early Detection: Early detection is critical. Recognition of changes in or the appearance of new skin growths is the best way to find early skin cancer. Basal and squamous cell skin cancers often take the form

of a pale, waxlike, pearly nodule, or a red scaly, sharply outlined patch. A sudden or continuous change in a mole's appearance should be checked by a physician. Melanomas often start as small, mole-like growths that increase in size, change color, become ulcerated and bleed easily from a slight injury. There is a simple ABCD rule that will help individuals remember the warning signs of melanoma: A is for asymmetry. One half of the mole does not match the other half. B is for border irregularity. The edges are ragged, notched or blurred. C is for color. The pigmentation is not uniform. D is for diameter greater than 6 millimeters. Any sudden or continuing increase in size should be of special concern.

Adults should practice skin self-examination once a month.

Treatment: There are four methods of treatment: surgery (used in 90% of cases), radiation therapy, electrodesiccation (tissue destruction by heat), or cryosurgery (tissue destruction by freezing) for early skin cancer.

For malignant melanoma, adequate surgical excision of the primary growth is indicated. Nearby lymph nodes may be removed. The microscopic examination of all suspicious moles is essential. Advanced cases of melanoma are treated on an individual basis.

Survival: For basal cell and squamous cell cancers, cure is highly likely with early detection and treatment. Malignant melanoma can spread to other parts of the body quickly. However, when detected in its earliest stages, with proper treatment, it is highly curable.

The overall 5-year survival rate for white patients with malignant melanoma is 80% compared with 95% for patients with other kinds of skin cancer. The 5-year survival rate for localized malignant melanoma is 89%; however, the survival rate, once melanoma has spread, is 39%.

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PANCREATIC CANCER

Incidence: An estimated 27,000 new cases in the United States in 1989. Pancreatic cancer is the 5th leading cancer killer. The incidence rate of pancreatic cancer among U.S. blacks is about 1.5 times higher than for whites.

Mortality: An estimated 25,000 deaths in 1989 due to pancreatic cancer. From 1954 to 1984, the death rates for pancreatic cancer in the United States rose 12% to 10.2 deaths per 100,000 men. During the same period, the death rates for women rose 26% to 7.2 deaths per 100,000 women.

Warning Signals: Cancer of the pancreas is a "silent" disease, one that occurs without symptoms until it is advanced.

Risk Factors: Fisk increases with age after age 30, with the highest frequency of incidence occurring between ages 65 and 79. Smoking is a major risk factor, incidence is more than twice as high for smokers versus nonsmokers. The disease is 30% more common in men, and occurs about 50% more frequently in black, versus white Americans. Some studies, as yet unconfirmed, suggest an association with chronic pancreatitis, dia-

betes and cirrhosis. High-fat diets may be a risk factor, countries with higher fat consumption levels have higher pancreatic cancer rates. Coffee has been investigated as a possible risk factor, but no conclusive evidence is currently available.

Early Detection: Research has focused on ways to diagnose pancreatic cancer before it is advanced enough to cause symptoms. Ultrasound and CT scans are being tried, but to date only a biopsy yields a certain diagnosis.

Prevention: Very little is known about what causes the disease, or how to prevent it.

Treatment: Surgery, radiation therapy and anti-cancer drugs are used to treat pancreatic cancer, but so far have had little influence on outcome. In 59% of cases, diagnosis is so late that none of these is used.

Survival: Only 4% of patients live more than 3 years after diagnosis. The 2% of patients whose cancers occur in the insulin-producing cells, and not the duct cells of the pancreas tend to live longer; about 30% of these patients live more than 3 years after diagnosis.

LEUKEMIA

Incidence: An estimated 27,300 new cases in 1989, about half of them acute leukemia, and half of them chronic leukemia. Although it is often thought of as primarily a childhood disease, leukemia strikes many more adults (25,000 cases per year compared with 2,300 in children). Acute lymphocytic leukemia accounts for about 1,800 of the cases of leukemia among children, whereas in adults the most common types are acute granulocytic (about 8,000 cases annually), and chronic lymphocytic (9,600 cases annually).

Mortality: An estimated 18,100 deaths in 1989.

Warning Signals: Symptoms of acute leukemia in children can appear suddenly. Early signs may include fatigue, paleness, weight loss, repeated infections, easy bruising, nose bleeds or other hemorrhages. Chronic leukemia can progress slowly and with few symptoms.

Risk Factors: Leukemia, a cancer of the bloodforming tissues, strikes both sexes and all ages. Causes of most cases are unknown. Individuals with Down's syndrome (mongolism) and certain other hereditary abnormalities have higher than normal incidence of leukemia. It has also been linked to excessive exposure to radiation and certain chemicals such as benzene.

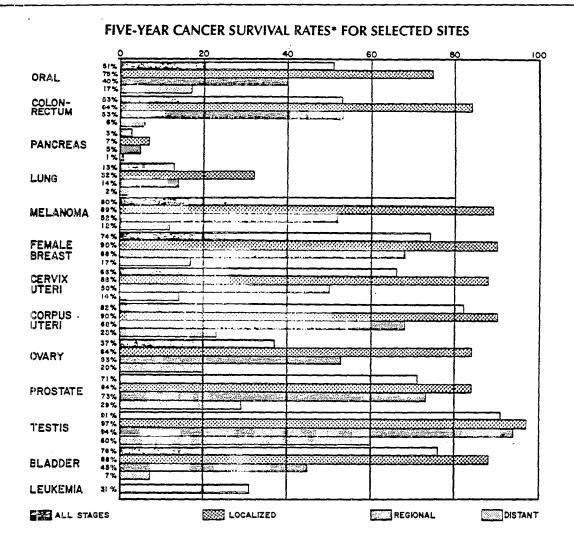
Early Detection: Leukemia may be difficult to diagnose early because symptoms often appear to be those of other less serious conditions. When a physician does suspect leukemia, a diagnosis can be made through blood tests and an examination of bone marrow.

Treatment: Chemotherapy is the most effective method of treating leukemia. Today, continuing research in leading U.S. medical centers is yielding new and better

drugs for treating leukemia patients. A variety of anticancer drugs are used, either in combinations or as single agents. To prevent persistence of hidden cells, therapy of the central nervous system has become standard treatment, especially in acute lymphocytic leukemia. Under appropriate conditions, bone marrow transplantation may be useful in the treatment of certain leukemias.

When leukemia occurs, millions of abnormal, immature white blood cells are released into the circulatory systems. These abnormal cells crowd out normal white cells to fight infection, platelets to control hemorrhaging and red blood cells to prevent anemia. Transfusions of blood components and antibiotics are used as supportive treatments.

Survival: The overall, average 5-year survival rate for white patients with leukemia is 33%, due partly to very poor survival of patients with some types of leukemia such as acute granulocytic. The 5-year survival rate for black patients is 28%. Over the last 30 years, however, there has been a dramatic improvement in survival of patients with acute lymphocytic leukemia: From a 5-year survival of 4% for white males diagnosed in the early 1960's to 27% in the early 1970's to 46% around 1980; for white females diagnosed in the same time periods, from 3% to 29% to 52%. In white children, the improvement has been from 4% to 68%. Moreover, in some medical centers, optimum treatment has raised survival of children with acute lymphocytic leukemia up to 75%.



^{*}Adjusted for normal life expectancy.
This chart is based on cases diagnosed in 1979-1984.

Source: Surveillance and Operations Research Branch, National Cancer Institute.

HOW TO ESTIMATE CANCER STATISTICS LOCALLY

| Community Population | Estimated No. Who Are Alive, Saved from Cancer | | Estimated No. Who Will Die of Cancer in 1989 | Estimated No. of New Cases in 1989 | Estimated No. Who Will Be Saved from Cancer in 1989 | Estimated No. Who Will Eventually Develop Cancer | Estimated No. Who Will Die of Cancer if Present Rates Continue |
|-------------------------|---|-------|---|---|---|--|--|
| 1,000 | 10 | 5 | 1 | 3 | 1 | 280 | 180 |
| 2,000 | 20 | 11 | 4 | 7 | 3 | 560 | 360 |
| 3,000 | 30 | 16 | 5 | 10 | 4 | 840 | 540 |
| 4,000 | 40 | 21 | 7 | 13 | 5 | 1,120 | 720 |
| 5,000 | 50 | 26 | 9 | 16 | 6 | 1,400 | 900 |
| 10,000 | 100 | 52 | 18 | 33 | 12 | 2,800 | 1,800 |
| 25,000 | 250 | 131 | 45 | 79 | 30 | 7,000 | 4,500 |
| 50,000 | 500 | 262 | 90 | 158 | 59 | 14,000 | 9,000 |
| 100,000 | 1,000 | 525 | 180 | 325 | 122 | 28,000 | 18,000 |
| 200,000 | 2,000 | 1,050 | 360 | 650 | 244. | 56,000 | 36,000 |
| 500,000 | 5,000 | 2,625 | 900 | 1,575 | 590 | 140,000 | 90,000 |

NOTE: The figures can only be the roughest approximation of actual data for your community and should be used with caution. It is suggested that every effort be made to obtain actual data from a Registry source.

CANCER BY AGE AND RACE*

BLACK AMERICANS

A study of cancer rates over several decades shows that the cancer incidence rate for blacks is higher than for whites, and that the death rate is also higher. Over a 30-year period, black male cancer death rates rose by 77% compared to a 10% increase in black females. Incidence rates in blacks also have increased in both males and females.

The overall cancer incidence rate for blacks went up 27%, while for whites it increased 12%. Cancer mortality has increased in both races, but the rate for blacks is greater than for whites. The rates were virtually the same 30 years ago. Since then, cancer death rates in whites have increased 10%, while black rates have increased almost 50%.

Cancer sites where blacks had significantly higher increases in incidence and mortality rates included the lung, colon-rectum, prostate and esophagus. Esophageal cancer, long considered mainly a disease of males, remained about the same in whites and rose rapidly in blacks of both sexes.

The incidence of invasive cancer of the uterine cervix

dropped in both black and white women, although the incidence in blacks is still double that in whites. However, the rate for endometrial cancer—or cancer of the body of the uterus—for white women is almost double that of black women.

Survival rates for patients diagnosed between 1974 and 1982 were compared for whites and blacks. More whites than blacks had cancer diagnosed in an early, localized stage when the chances of cure are best: 39% for whites versus 33% for blacks.

In a survey done for the ACS by the Gallup Organization in December 1987, the public's awareness and use of cancer tests was determined. The survey showed that 93% of white women knew of the Pap test and that 88% had had the test at some time, while 92% of black women knew of it and 79% had had it. For proctoscopic exams, 60% of the white population were aware of the procedure and 29% had had it at some time. For blacks, only 49% were aware of it and 22% had had it.

THE ECONOMICALLY DISADVANTAGED

A 1986 ACS Special Subcommittee report, "Cancer in the Economically Disadvantaged" found that cancer survival, and in some cases incidence, are related to socioeconomic factors such as the availability of health services. The report also found that ethnic differences in cancer are secondary to socioeconomic factors, and that there are higher rates of cancer mortality for

patients of low socioeconomic status compared to those in higher brackets. Estimates suggest that at least half of the differences in survival rates are due to late diagnosis among economically disadvantaged patients, pointing up the need for more effective early detection programs and better access to treatment among this segment of the American population.

HISPANIC-AMERICANS

A recent ACS-sponsored report described Hispanic attitudes toward cancer, cancer risk reduction and early detection. The study, conducted for the Society by the firm of Clark, Martire and Bartolomeo, Inc., underscored an urgent need for extensive cancer education and information programs directed to Hispanic-Americans. Survey findings showed that Hispanic-Americans are

not adequately aware of most of the warning signals of cancer or of ways to reduce cancer risk, and that they tend not to seek early detection or treatment. The study identified the key psychological, cultural and economic barriers hindering the fight against cancer in the Hispanic-American community.

CHILDREN

Incidence: An estimated 6,600 new cases in 1989, making it rare as a childhood disease. Common sites include the blood and bone marrow, bone, lymph nodes, brain, nervous system, kidneys and soft tissues.

Mortality: An estimated 1,800 deaths in 1989, about half of them from leukemia. Despite its rarity, cancer is the chief cause of death by disease in children between the ages of 3 and 14. Mortality has declined from 8.3 per 100,000 in 1950 to 3.5 in 1986.

Early Detection: Cancers in children often are difficult to recognize. Parents should see that their children have regular medical checkups, and be alert

to any unusual symptoms that persist. They include: unusual mass or swelling; unexplained paleness and loss of energy; sudden tendency to bruise; persistent, localized pain or limping; prolonged, unexplained fever or illness; frequent headaches, often with vomiting; sudden eye or vision changes; and excessive, rapid weight loss.

Some of the main childhood cancers are:

Leukemia: See preceding section.

Osteogenic Sarcoma and Ewing's Sarcoma are bone cancers. There may be no pain at first, but swelling in the area of the tumor is often a first sign.

CANCER BY AGE AND RACE

Neuroblastoma can appear anywhere but usually in the abdornen, where a swelling occurs.

Rhabdomyosarcoma, the most common soft tissue sarcoma, can occur in the head and neck area, genito-urinary area, trunk and extremities.

Brain Cancers in early stages may cause headaches, blurred or double vision, dizziness, difficulty in walking or handling objects, and nausea.

Lymphonus, and Hodgkin's Disease are cancers that involve the lymph nodes, and also may invade bone marrow and other organs. They may cause swelling of lymph nodes in the neck, armpit or groin. Other symptoms may include general weakness and possibly fever.

Retinoblastoma, or an eye cancer, usually occurs in

children under the age of four. When detected early, cure is possible with appropriate treatment.

Wilms' Tumor, a kidney cancer, may be recognized by a swelling or lump in the abdomen.

Treatment: Childhood cancers can be treated by a combination of therapies, coordinated by a team of experts. They include oncologic physicians, pediatric nurses, social workers, psychologists and others who assist children and their families.

Survival: Five-year survival rates vary considerably, depending on the site. Among those for white children: bone cancer, 48%; neuroblastoma, 56%; brain and central nervous system, 56%; Wilms' tumor (kidney), 82%; and Hodgkin's disease, 91%. (Data for black children is insufficient.)

TRENDS IN SURVIVAL BY SITE OF CANCER, BY RACE Cases Diagnosed in 1960-63, 1970-73, 1974-76, 1977-78, 1979-84

| | | | WHITE | | | | | BLACK | | |
|-------------------------|--------------------------|----------|------------|------------|-------------------|--------------------------|----------|-------------|----------|----------|
| | RELATIVE 5-YEAR SURVIVAL | | | | | RELATIVE 5-YEAR SURVIVAL | | | | |
| SITE | 1960-631 | 1970-731 | 1974-762 | 1977-782 | 1979-842 | 1960-631 | 1970-731 | 1974-762 | 1977-782 | 1979-842 |
| All Sites | 39% | 43% | 50% | 50% | 50% | 27% | 31% | 38% | 38% | 37% |
| Oral Cavity & Pharynx . | 45 | 43 | 54 | 53 | 54 | - | - | 35 | 35 | 31 |
| Esophagus | 4 | 4 | 5 | 6 | 7 | 1 | 4 | 4 | 2 | 5 |
| Stomach | 11 | 13 | 14 | 15 | 16* | 8 | 13 | 15 | 16 | 17 |
| Colon | 43 | 49 | 50 | 5 2 | 54° | 34 | 37 | 45 | 44 | 49 |
| Rectum | 38 | 45 | 48 | 50 | 52° | 27 | 30 | 40 | 40 | 34 |
| Liver | 2 | 3 | . 4 | . 3 | 3 | - | - | 1 | 1 | 5 |
| Pancreas | 1 | 2 | 3 | 2 | 3 | 1 | 2 | 2 | 3 | 5 |
| Larynx | 53 | 62 | 66 | 69 | ,6 6 . | - | - | 58 | 59 | 55 |
| Lung & Bronchus | 8 . | 10 | 12 | 13 | 13* | 5 | 7 | 71 | 10 | 11 |
| Melanoma of Skin | 60 | 68 | 78 | 81 | 80* | - | - | 62## | - | 61# |
| Breast (females) | 63 | 68 | 74 | <i>7</i> 5 | 75° | 46 | 51 | 62 | 62 | 62 |
| Cervix Uteri | 58 | 64 | 69 | 69 | 67 | 47 | 61 | 61 | 63 | 59 |
| Corpus Uteri | 73 | 81 | 89 | 87 | 83* | 31 | 44 | 61 | 58 | 52* |
| Ovary | 32 | 36 | 36 | 37 | 37* | 32 | 32 | 41 | 40 | 36 |
| Prostate Gland | 50 | 63 | 67 | 70 | <i>7</i> 3* | 35 | 55 | 56 | 64 | 60* |
| Testis | 63 | 72 | <i>7</i> 8 | 86 | 91* | - | - | <i>77</i> # | _ | 82# |
| Urinary Bladder | 53 | 61 | <i>7</i> 3 | <i>7</i> 5 | 77* | 24 | 36 | 47 | 53 | 57* |
| Kidney & Renal Pelvis | 37 | 46 | 51 | 50 | 51 | 38 | 44 | 49 | 54 | 53 |
| Brain & Nervous System | 18 | 20 | 22 | 23 | 23 | 19 | 19 | 27 | 24 | 31 |
| Thyroid Gland | 83 | 86 | 92 | 92 | 93 | - | - | 88 | 92 | 95 |
| Hodgkin's Disease | 40 | 67 | 71 | 73 | 74* | - | - | 67# | 79# | 69 |
| Non-Hodgkin's Lymphoma | 31 | 41 | 47 | 48 | 49* | ! - | - | 47 | 46 | 49 |
| Multiple Myeloma | 12 | 19 | 24 | 24 | 24 | - | _ | 28 | 30 | 29 |
| Leukemia | 14 | 22 | 34 | 37 | 32 | - | - | 30 | 31 | 27 |

Source: Surveillance and Operations Research Branch, National Cancer Institute.

^{*}Figures for cancer incidence are from the National Cancer Institute National Surveys, 1947, and the NCI SEER Program, 1973-1985; those for cancer mortality are from the National Center for Health Statistics, 1953-55 to 1983-85.

¹ Rates are based on End Results Group data from a series of hospital registries and one population-based registry.

² Rates are from the SEER Program. They are based on data from population-based registries in Connecticut, New Mexico, Utah, Iowa, Hawaii, Atlanta, Detroit, Seattle-Puget Sound and San Francisco-Oakland. Rates are based on follow-up of patients through 1985.

 $^{^{\}circ}$ The difference in rates between 1974-76 and 1979-84 is statistically significant (p < .05).

[#] The standard error of the survival rate is between 5 and 10 percentage points.

^{##} The standard error of the survival rate is greater than 10 percentage points.

Valid survival rate could not be calculated.

| | PREVENTION |
|----------------------------|---|
| | PRIMARY PREVENTION REFERS TO STEPS THAT MIGHT BE TAKEN TO AVOID THOSE FACTORS THAT MIGHT LEAD TO THE DEVELOPMENT OF CANCER. |
| SMOKING | Cigarette smoking is responsible for 85% of lung cancer cases among men and 75% among women—about 83% overall. Smoking accounts for about 30% of all cancer deaths. Those who smoke two or more packs of cigarettes a day have lung cancer mortality rates 15 to 25 times greater than nonsmokers. |
| SUNLIGHT | Almost all of the more than 500,000 cases of non-melanoma skin cancer developed each year in the U.S. are considered to be sun-related. Recent epidemiological evidence shows that sun exposure is a major factor in the development of melanoma and that the incidence increases for those living near the equator. (See Selected Cancer Sites: Skin Cancer) |
| ALCOHOL | Oral cancer and cancers of the larynx, throat, esophagus, and liver occur more frequently among heavy drinkers of alcohol. (See Selected Cancer Sites: Oral Cancer) |
| SMOKELESS TOBACCO | Increased risk factor for cancers of the mouth, larynx, throat, and esophagus. Highly habit forming. (See Selected Cancer Sites: Lung Cancer and Oral Cancer) |
| ESTROGEN | For mature women, certain risks associated with estrogen treatment to control menopausal symptoms, including an increased risk of endometrial cancer. Use of estrogen by menopausal women needs careful discussion by the woman and her physician. (See Selected Cancer Sites: Uterine Cancer) |
| RADIATION | Excessive exposure to radiation can increase cancer risk. Most medical X rays are adjusted to deliver the lowest dose possible without sacrificing image quality. The ACS believes there is a potential problem of radon in the home. If levels are found to be too high, remedial actions should be taken. |
| OCCUPATIONAL HAZARDS | Exposure to a number of industrial agents (nickel, chromate, asbestos, vinyl chloride, etc.) increases risk. Risk factor greatly increased when combined with smoking. |
| NUTRITION | Risk for colon, breast and uterine cancers increases for obese people. High-fat diet may be a factor in the development of certain cancers such as breast, colon and prostate. High-fiber foods may help reduce risk of colon cancer, and can be a wholesome substitute for high-fat diets. Foods rich in vitamins A and C may help lower risk for cancers of larynx, esophagus, stomach and lung. Eating cruciferous vegetables may help protect against certain cancers. Salt-cured, smoked and nitrite-cured foods have been linked to esophageal and stomach cancer. The heavy use of alcohol, especially when accompanied by cigarette smoking or chewing tobacco, increases risk of cancers of the mouth, larynx, throat, esophagus, and liver. (See above) |
| | SECONDARY PREVENTION REFERS TO STEPS TO BE TAKEN TO DIAGNOSE A CANCER OR PRECURSOR AS EARLY AS POSSIBLE AFTER IT HAS DEVELOPED. |
| COLORECTAL TESTS | The ACS recommends three tests for the early detection of colon and rectum cancer in people without symptoms. The digital rectal examination, performed by a physician during an office visit, should be performed every year after the age of 40; the stool blood test is recommended every year after 50; and the proctosigmoidoscopy examination should be carried out every 3 to 5 years after the age of 50 following two annual exams with negative results. (See Selected Cancer Sites: Colon and Rectum Cancer) |
| PAP TEST | For cervical cancer, women who are or have been sexually active, or have reached age 18 years, should have an annual Pap test and pelvic examination. After a woman has had three or more consecutive satisfactory normal annual examinations, the Pap test may be performed less frequently at the discretion of her physician. |
| BREAST CANCER DETECTION | The ACS recommends the monthly practice of breast self-examination (BSE) by women 20 years and older as a routine good health habit. Physical examination of the breast should be done every three years from ages 20-40 and then every year. The ACS recommends a mammogram every year for asymptomatic women age 50 and over, and a baseline mammogram between ages 35 and 39. Women 40 to 49 should have mammography every 1-2 years, depending on physical and mammographic findings. |

CANCER-RELATED CHECKUP GUIDELINES

Guidelines for the early detection of cancer in people without symptoms are recommended by the American Cancer Society as follows:

A cancer-related checkup:

every 3 years for those 20-40 years of age.

every year for those 40 and over.

The Society advises that you talk with your doctor. Ask how the guidelines apply to you. The checkup should always include health counseling (such as tips on quitting smoking) and examinations for cancer of the thyroid, testes, prostate, mouth, ovaries, skin and lymph nodes.

In particular:

• Ages 20-40—For breast cancer, an examination by a physician every three years, a self-exam every month, and one baseline breast X ray between the ages of 35 and 39. For cervical cancer, women who are or have been sexually active, or have reached age 18, should have an annual Pap test and pelvic examination. After a woman has had three or more consecutive satisfactory

normal annual examinations, the Pap test may be performed less frequently at the discretion of her physician. Ages 40 and over—For breast cancer, a professional exam every year, a self-exam every month and a breast X ray every 1-2 years for those 40-49; every year for those 50 and over. For cervical cancer, women who are or have been sexually active, or have reached age 18 years, should have an annual Pap test and pelvic examination. After a women has had three or more consecutive satisfactory normal annual examinations, the Pap test may be performed less frequently at the discretion of her physician. For women at risk, an endometrial tissue sample at menopause should be taken. For colon and rectum cancer, a digital rectal exam every year after 40, and a stool blood test every year after 50 as well as a procto exam every 3-5 years after two initial negative tests one year apart.

Some people are at higher risk for certain cancers and may need tests more frequently. (See pp. 9-14 for high risk factors.)

COLORECTAL CANCER: EARLY DETECTION IS THE KEY

When cancer of the colon and rectum is found and treated in an early, localized stage, the 5-year survival rate is 90% for colon cancer and 80% for rectal cancer. However, survival figures drop to 40% and 31%, respectively, after the cancer has started to spread to other parts of the body.

Because colorectal cancer develops over a period of time, detection of the disease is possible long before symptoms appear. Early detection of small cancers and polyps reduces the likelihood of major surgery and the need for a colostomy—an abdominal opening created for the elimination of wastes. In fact, permanent colostomies are rare in cases of colon cancer, and are neces-

sary in only 15% of rectal cancer cases.

Colorectal cancer is second only to lung cancer in terms of incidence. Currently, about 151,000 new cases develop each year; about 61,000 people die from the disease annually. The incidence of colorectal cancer tends to increase with age, starting at 40 years. More than 94% of all cases occur after the age of 50. Colorectal cancer occurs about equally in both sexes. Anyone with a personal or family history of colorectal cancer, polyps in the colon or inflammatory bowel disease, is at particularly high risk for the disease and should be examined carefully.

Evidence suggests that bowel cancer may be linked to a diet high in fat and/or low in fiber content.

Projected 5-year survival rates for colorectal cancer show that early detection saves lives. Currently, the 5-year survival rate is estimated at 55%. With the use of early detection techniques, such as the digital rectal exam, the stool blood test and sigmoidoscopy, and with appropriate management, the survival rate for patients with colorectal cancer could be increased from 55% to 85%. This means that, over a period of time, 125,000 lives, versus the current 80,000, could be saved each year.

It is recommended that the following procedures, all part of a cancer-related checkup, be performed at designated intervals:

- A digital rectal examination every year after age 40.
- A stool blood test every year after age 50.

• A procto every three to five years after the age of 50, following two annual negative examinations.

These guidelines apply only to people without symptoms. Persons with rectal bleeding, cramping abdominal pain, or a change in bowel habits should see their physicians immediately.

A 1987 study of men and women age 40 and over, conducted for the Society by the Gallup Organization, revealed a number of important findings concerning Americans' attitudes toward detection measures for colorectal cancer. There has been some increase in public awareness of the 3 tests recommended to detect the disease, but there is much room for improvement. The study found, for instance, that the percentage of Americans who ever had a digital rectal examination increased slightly since 1983, from 51% to 56%. Likewise, the percentage of Americans who ever had a stool blood test rose, from 28% in 1983 to 40% in 1987. And while the percentage of men and women 50 and over who ever had a proctoscopic examination rose from 31% in 1983 to 42% in 1987, 60% of Americans who should have the examination (according to the ACS guidelines) have not had it.

The survey also showed that 24% of those individuals in the 40-plus age group have ever asked their doctor to examine their colon or rectum. And of this group, more than half did so only because something was bothering them.

On the promising side, the survey showed that almost 50% of all Americans would be interested in learning more about this form of cancer.

BREAST CANCER: A PROGRAM OF ACTION

About one out of every 10 women in the United States will develop breast cancer during her lifetime. And until the disease can be prevented, the best way women can protect themselves is through early detection and prompt treatment. Today, with modern technologies, breast cancer can be detected at very early stages of development, when the chance of cure is highest.

The risk of breast cancer increases as a woman grows older, and genetic and lifestyle variances—a history of breast cancer in a close family relative, giving first birth after age 30, never giving birth, and obesity (body weight 40% above normal)—may increase risk further.

The American Cancer Society recommends that women develop a three-part, personal plan of action, in cooperation with their doctors for early detection of breast cancer. (See page 19 for Checkup Guidelines.)

A clinical breast exam should be performed by a doctor as part of a regular health checkup. This includes

a visual inspection of the breasts, looking for changes in shape or size or skin dimpling, followed by a thorough inspection of the breast, chest and armpits. Women should ask their doctors how often they should have a clinical breast exam.

A mammogram is a low-dose breast X ray that can identify cancers too small to be felt. Follow the ACS guidelines for recommended frequency, depending on age and health history. Recent improvements have reduced the amount of radiation necessary for high-quality mammograms.

The Society recommends that all women over the age of 20 perform breast self-examination once a month. BSE is important because breast cancer symptoms may develop and be found between clinical breast exams or mammography. Through regular self-examination women become familiar with their breasts, making any changes more likely to be noticed.

TOBACCO USE

The American Cancer Society estimates that cigarette smoking is responsible for 85% of lung cancer cases among men and 75% among women—about 83% overall.

The cancer death rate for male cigarette smokers is more than double that of nonsmokers, and the rate for female smokers is 67% higher than for nonsmokers. The American Caricer Society estimates that 40% of male smokers and 28% of female smokers die prematurely, or about 35% overall.

The higher cancer rates for men reflect the fact that in the past, more men than women smoked, and smoked more heavily. In recent years, however, the gap between male and female smoking has been narrowing.

Smoking also has been implicated in cancers of the mouth, pharynx, larynx, esophagus, pancreas, cervix uteri and bladder. Smoking accounts for about 30% of all cancer deaths, is a major cause of heart disease, and is linked to conditions ranging from colds and gastric ulcers to chronic bronchitis and emphysema.

Smoking is related to 390,000 deaths each year. A September 1985 study by the U.S. Congress Office of Technology Assessment estimates the cost of smoking to the economy from \$38 billion to \$95 billion, with a middle estimate of \$65 billion. This amounts to \$2.17 in lost productivity and the treatment of smoking-related diseases for each pack of cigarettes sold.

A Decline in Smoking

A September 1987 tobacco report of the U.S. Department of Agriculture estimates cigarette output in 1987 at 654 billion, down 1.0% from 1986, about the same decrease as the previous year.

From 1976 to 1987, adult male smokers (20 years and older) dropped from 42% of the population to 33%, while women smokers decreased from 32% to 28%, according to the National Center for Health Statistics. Overall,

the percentage of adult smokers in the population had dropped to 30%. A 1987 report from the Office of Smoking and Health says that 26.5% of Americans now smoke.

Per capita cigarette consumption among adults has fallen—from 4,141 in 1974 to 3,121 in 1988—reflecting a growing number of ex-smokers. This is the lowest per capita consumption since 1944. From 1965 to 1987, the proportion of adult male ex-smokers (20 years and older) in the total U.S. population increased from 20% to 31%, while female ex-smokers rose from 8% to 19%.

A survey supported by the National Institute on Drug Abuse indicated that the percentage of high school seniors (aged 17 and 18) who smoked cigarettes daily decreased from 29% in 1976 to 19% in 1987.

It is now estimated—from past national surveys and data from the Cancer Prevention Study II—that there are about 40 million ex-cigarette smokers in the U.S. today and about 50 million smokers.

At the same time, however, the average smoker appears to be smoking more heavily. The U.S. Office on Smoking and Health reports that the proportion of adult male smokers (20 years and older) consuming 25 or more cigarettes per day increased from 30.7% to 32% between 1976 and 1985, and female smokers from 19.0% to 21%.

Figures from the U.S. Department of Agriculture show that a total of 567 billion cigarettes were consumed in 1988, down from 575 billion in 1987.

Nicotine Addiction

The Surgeon General released a report on nicotine addiction in May 1988. The report points out that all tobacco products contain substantial amounts of nicotine. Nicotine is absorbed readily from tobacco smoke in the lungs and from smokeless tobacco in the mouth or nose, and is rapidly distributed throughout

the body. The conclusions were:

1) Cigarettes and other forms of tobacco are addicting;

2) Nicotine is the drug in tobacco that causes addiction; and 3) The pharmacologic and behavioral processes that determine tobacco addiction are similar to those that determine addiction to drugs such as heroin and cocaine.

Lower Tar & Nicotine

Research has shown that there is no such thing as a "safe" cigarette, but that those who are not yet able to quit would be well advised to switch to brands with the lowest possible tar and nicotine (T/N) content. Moreover, low T/N smokers find it easier to quit altogether than high T/N smokers.

In an ACS study conducted from 1960 to 1972, the average mortality of low T/N smokers was 16% lower than that of high T/N smokers, and the comparable figure for lung cancer mortality was 26%.

It is important to remember that besides tar and nicotine, cigarette smoke contains a host of other poisonous gases such as hydrogen cyanide, volatile aromatic hydrocarbons, and especially carbon monoxide—possibly a critical factor in coronary heart disease and fetal growth retardation. While some hazards are reduced slightly by cigarette filters, certain filtered brands have been found to actually deliver more carbon monoxide than those without filters.

Involuntary Smoking Hazards

There are hazards for nonsmokers who breathe the smoke of others' cigarettes. Several scientific studies, including a recent study by the American Cancer Society, have found an increased risk of lung cancer among nonsmoking wives of cigarette smokers. Although some studies have not shown an effect, evidence continues to grow indicating that involuntary smoking is a hazard.

Two major reviews in 1986 by the Surgeon General and the National Academy of Sciences state that involuntary smoking is a health hazard. Another NAS report, also in 1986, states that the amount of smoke inhaled on airplane trips constitutes a hazard, partic-

ularly to airline personnel, and recommended that cigarette smoking on airlines be banned.

The Society's Cancer Prevention Study II, involving more than one million Americans, will include a careful assessment of cancer risk and other diseases among smokers and involuntary smokers.

Smokeless Tobacco

There has been a recent resurgence in the use of all forms of smokeless tobacco—plug, leaf and snuff but the greatest cause for concern centers on the increased use of "dipping snuff." In this practice, tobacco that has been processed into a coarse, moist powder is placed between the cheek and gum, and nicotine, along with a number of other carcinogens, are absorbed through the oral tissue. "Dipping snuff" is a highly addictive habit, one that exposes the body to levels of nicotine similar to those of cigarettes. A 1986 report of the Advisory Committee to the Surgeon General, outlining the health consequences of smokeless tobacco use, concluded that there is strong scientific evidence that the use of snuff causes cancer in humans, particularly cancer of the oral cavity. Oral cancer occurs several times more frequently among snuff dippers compared to non-tobacco users, and the excess risk of cancer of the cheek and gum may reach nearly 50-fold among long-term snuff users. Smokeless tobacco is becoming a problem large in scope; the report found that in 1985 smokeless tobacco was used by at least 12 million people in the United States, and half of these were regular users. The use of smokeless tobaccos is increasing among male adolescents and young male adults.

Industrial Hazards

Industrial workers are especially susceptible to lung diseases due to the combined effects of cigarette smoking and exposure to toxic industrial substances such as fumes from rubber, chlorine and dust from cotton and coal. Exposure to asbestos in combination with cigarette smoking increases an individual's lung cancer risk nearly 60 times.

NUTRITION AND CANCER: A COMMON SENSE APPROACH

Extensive research is under way to evaluate and clarify the role diet and nutrition play in the development of cancer. At this point, no direct cause-and-effect relationship has been proved, though statistics show that some foods may increase or decrease the risks for certain types of cancer. Evidence indicates that people might reduce their cancer risk by observing the following recommendations:

1. Avoid obesity.

Individuals 40% or more overweight increase their risk of colon, breast, prostate, gallbladder, ovary, and

uterine cancers. People with weight problems should consult their physicians to determine their best body weight, since their medical condition and body build must be taken into account. Physicians can recommend a suitable diet and exercise regimen to help maintain an appropriate weight.

2. Cut down on total fat intake.

A diet high in fat may be a factor in the development of certain cancers, particularly breast, colon and prostate. In addition, by avoiding fatty foods, people are better able to control body weight.

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3. Eat more high-fiber foods such as whole grain cereals, fruits and vegetables.

Regular consumption of cereals, fresh fruits and vegetables is recommended. Studies suggest that diets high in fiber may help to reduce the risk of colon cancer. Furthermore, foods high in fiber content are a wholesome substitute for foods high in fat.

4. Include foods rich in vitamins A and C in your daily diet.

People should include in their diet dark green and deep yellow fresh vegetables and fruits, such as carrots, spinach, sweet potatoes, peaches, and apricots as sources of vitamin A; and oranges, grapefruit, strawberries, green and red peppers for vitamin C. These foods may help lower risk for cancers of the larynx, esophagus and the lung. The excess use of vitamin A supplements is not recommended because of possible toxicity.

5. Include cruciferous vegetables in your diet.

Certain vegetables in the cruciferous family-

cabbage, broccoli, brussels sprouts, kohlrabi and cauliflower—may help prevent certain cancers from developing. Research is in progress to determine how these foods may protect against cancer. Cruciferous vegetables have flowers with four leaves in the pattern of a cross.

6. Eat moderately of salt-cured, smoked and nitrite-cured foods.

In areas of the world where salt-cured and smoked foods are eaten frequently, there is more incidence of cancer of the esophagus and stomach. The American food industry has developed new processes to avoid possible cancer-causing by-products.

7. Keep alcohol consumption moderate, if you do drink.

The heavy use of alcohol, especially when accompanied by cigarette smoking or smokeless tobacco, increases risk of cancers of the mouth, larynx, throat, esophagus and liver.

CANCER FACTS AND FIGURES 1989

THE AMERICAN CANCER SOCIETY

PROFILE

The ACS traces its origins to 1913, when a group of ten physicians and five laymen met in New York City and founded the American Society for the Control of Cancer. Its stated purpose at the time was to "disseminate knowledge concerning the symptoms, treatment, and prevention of cancer; to investigate conditions under which cancer is found; and to compile statistics in regard thereto." Later renamed the American Cancer Society, it is today one of the oldest and largest voluntary health agencies in the United States, comprised of 2.5 million Americans united to conquer cancer through balanced programs of research, education, patient service and rehabilitation.

Organization: The American Cancer Society, Inc. is composed of a National Society, with 57 chartered Divisions and 3,232 Units.

The National Society: A 206-member House of Delegates provides a basic representation from the 57 Divisions and additional representation on the basis of population. It elects and is governed by a Board of Directors of 124 voting members, approximately half

of whom are members of the medical or scientific professions.

The National Society is responsible for overall planning and coordination, provides technical help and materials to Divisions and Units, administers programs of research, medical grants and clinical fellowships, and carries out public and professional education on the national level.

The 57 Divisions: These are governed by members of Divisional Boards of Directors, both medical and lay, in all the states plus five metropolitan areas, the District of Columbia and Puerto Rico.

The Units: These are organized to cover the counties in the United States. There are thousands of community leaders who direct the Society's programs at this level.

The Programs: The Society maintains its priorities and goals through activities developed by the departments of Research, Professional Education, Public Education, Public Information, Epidemiology and Statistics, Service and Rehabilitation, Public Affairs, and Crusade.

PUBLIC EDUCATION

The American Cancer Society has a strong and longstanding commitment to educating the public about ways of preventing or reducing the risk of developing cancer. Because each year thousands of lives could be saved through cancer prevention, risk reduction and early detection practices, the Society's Public Education programs are designed to inform people about cancer, tell them what they can do to protect

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themselves, and demonstrate related health habits and lifestyles.

The Society places its major educational focus in two areas: 1) primary cancer prevention which includes smoking control and the relationship between diet, nutrition and cancer; and 2) the importance and value of periodic, cancer-related checkups and specific cancer early detection tests. Prompt action in the event that one of cancer's seven warning signals occurs, is also encouraged.

Six cancer sites offer the greatest opportunity for the prevention or cure of cancer: colon and rectum, lung, breast, uterus, oral cavity and skin. These sites account for the majority of cancer cases and about half of all cancer deaths. The Society's Public Education planning strategy places emphasis on these six sites where prevention, risk reduction and early detection practices realize the greatest return in terms of lives saved.

Educating the Young and Old

ACS Public Education programs are divided into two major audience categories: adults and youth. Adults are reached through their worksite, healthsite and community. Programs for adults are carried out in small group settings or on a one-to-one basis, involving two-way communication and interaction. Whenever possible, volunteers are selected on the basis of skills that can be readily adapted to Society work, such as ex-smokers with group experience who can help in smoking cessation programs, and nurses who can teach breast self-examination to groups of women. The Society reinforces its Public Education messages with a variety of audio-visuals, pamphlets and posters.

Youth programs are organized according to agelevel to reach children and youth on the pre-school, elementary, intermediate and secondary levels. The program for youth is a scientific, comprehensive cancer education program with promise of significant impact

on cancer risk. Educational strategies are designed to teach young people good health habits, help them to make health-enhancing lifestyle decisions and understand health behavior as it relates to cancer risk reduction. Materials are available as coordinated components or program packages and are implemented through existing school curricula or as a basic introduction to health. Youth programs are usually conducted in the nation's schools and often include activities to be used in the home and community.

Reaching More People

In 1987-88, American Cancer Society Public Education programs, carried out at local levels, reached 23 million adults and 27 million young people for a total of 50 million.

In the decade of the 1980's, the Society, as its goals, hopes to encourage more Americans to have tests for colorectal cancer, reduce the number of smokers, and increase the number of women who have breast cancer detection tests and who practice monthly breast selfexamination, get Pap tests and have endometrial tissue samples taken. To help achieve its education objectives and priorities, the Society has launched a number of programs including "Taking Control" and "Eating Smart" for a healthier life of reduced cancer risk; "Special Delivery, Smoke Free" for pregnant women who are smokers; "Starting Free, Good Air For Me" for preschool children; "Where There's No Smoke..." on involuntary tobacco smoke; and an educational emphasis on breast cancer detection awareness, "Special Touch."

In addition to the Society's intensive, person-toperson educational outreach, broader ACS programs blanket the nation with lifesaving messages. During the Society's annual door-to-door fund-raising Crusade, volunteers make personal home visits, informing individuals on how to protect themselves against

PROFESSIONAL EDUCATION

ACS Professional Education programs bring the latest developments in cancer control and management to health professionals, especially primary care providers.

Professional Education's National conferences, clinical awards, materials, professorships and scholarships provide information and training in the prevention and early detection of cancer, and in the treatment and rehabilitation of cancer patients. Breast Cancer Detection Awareness, Colorectal Health Check and Tobacco-Free Young America are among the major initiatives offered by Divisions and Units as interdepartmental collaboration promoted by Professional Education. Recruitment and involvement of health professionals into Professional Education remains a major objective, particularly primary care providers.

Audiovisuals, Journals, and Other Publications

Videotapes, films, slide sets, audiotapes, publications and exhibits are available for physicians and other health professionals as well as for programs in hospitals, medical, dental and nursing schools. The Society publishes several texts and pamphlets dealing with various cancer issues along with proceedings of its conferences and workshops. Audiovisuals and other publications are distributed through ACS Divisions and Units.

Ca-A Cancer Journal for Clinicians, (470,000 circulated) is directed to update health professionals about cancer. The Society supports the publication of Cancer, directed to those specializing in cancer research and in the care of the cancer patient.

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Nursing Programs

Cancer Nursing News is sent to about 90,000 nurses. It keeps nurses up-to-date on cancer, oncology nursing, the American Cancer Society, and opportunities in continuing education. The newsletter is sent free to any nurse; requests for subscriptions should be sent to the Executive Editor, Cancer Nursing News, c/o American Cancer Society, 1599 Clifton Road, N.E., Atlanta, GA 30329.

Twenty one-year nursing scholarships are awarded each year to qualified graduate students studying for a master's degree with a specialty in cancer nursing. The recipients may apply for a second year's funding. A training program to prepare nurses for Ph.D.'s in related fields was initiated with the funding of the first three candidates in 1986.

Professorships in Clinical Oncology

Leading experts in oncology are supported to promote cancer education in medical and health professional schools. Since the award's inception in 1970, the Society has funded 53 professors. Recently the program has expanded to fund its first Professor involved in Dental Oncology.

Clinical Oncology Awards

The ACS National Clinical Awards Program was established in 1948 to provide broad support for oncology training at qualified hospitals and institutions. Over the past 40 years, Regular Clinical Fellowships and Junior Faculty Clinical Fellowships have had considerable impact on the training of physicians and dentists in oncology specialties, training over 8,500 individuals to provide care to cancer patients nationwide.

The program has changed somewhat over time; the original awards have been modified based on changes in oncology over time. Currently, monies are provided via the Clinical Oncology Fellowships (COF) and Clinical Oncology Career Development Award (CDA).

The former program replaces the regular Clinical Fellowship and intends to provide unique training opportunities for fellows to expand their expertise in oncology. The CDA is awarded to outstanding individuals who have demonstrated a commitment to pursue an academic career in oncology.

For the first time, a traineeship is being offered for Oncology Social Workers committed to clinical practice and research to benefit cancer patients and their families. The first awards will be made in 1989 to 24 master's and post-master's candidates.

To meet the needs in cancer prevention and detection, the concept of a new career development award for primary care physicians is under consideration. When accepted, these awards will help develop academic leaders in primary care to promote lifesaving techniques to the critical specialties.

The implementation of training program support for allied health professionals is also being studied. By broadening and expanding our efforts in oncology training, the Society's long-term goal of promoting cancer education, cancer control and cancer management among all health care providers will be advanced.

Unproven Methods of Cancer Management

The American Cancer Society maintains information on unproven methods of cancer management. This information is reviewed in-depth and is issued in position statements. These statements are available on request to physicians, science writers, editors and the general public, to assist in evaluating claims made for unproven methods of diagnosis and treatment.

The Committee on Unproven Methods of Cancer Management has commissioned a survey to determine the prevalence of, reasons for use, and patterns of use of unproven methods by the cancer patient. The findings from this study will provide guidelines for future programs in unproven methods of cancer management.

SERVICE AND REHABILITATION

In 1988, over one-half million cancer patients were reached through the innovative service and rehabilitation programs of the American Cancer Society. Because of the many volunteers at the Division and Unit levels, the Society is able to offer a wide range of services.

Service Programs

Resources Information and Guidance Services. Specific information is provided about cancer, as well as referral to Society services and other resources in the community to meet the social, psychological and home care needs of cancer patients and their families.

Home Care Items. This program provides necessary

useful home care supplies, equipment, dressings and gifts for the comfort and recreation of the patient.

Transportation. Through the efforts of volunteer drivers in programs such as Road to Recovery, transportation is provided to patients, enabling them to maintain their medical and continuing care programs.

Rehabilitation Programs

CanSurmount. This is a short-term visitor program for patients, and the families of patients, with many types of cancer. Hospital and home visits are made with the approval of the physician. The one-to-one visit by a person who has experienced the same type of cancer offers functional, emotional and social support.

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Reach to Recovery. This program, the largest of the Society's patient visitor programs, addresses the many needs of women who have or have had breast cancer. Carefully selected and trained volunteer visitors provide support and information, with the approval of the attending physician. The program is designed to help women meet the physical, emotional, and cosmetic needs related to their disease and/or its treatment. In addition, literature and services to help husbands, children and friends of breast cancer patients are available.

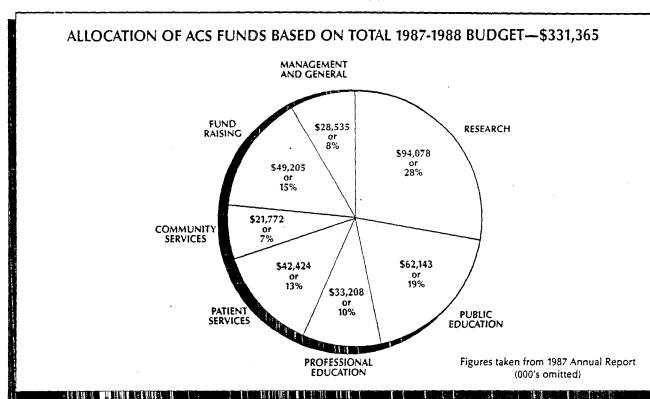
Laryngectomy Rehabilitation. Spearheaded by the International Association of Laryngectomees (IAL), this program brings the message that a laryngectomee can return to a normal life. Coordinated through more than 325 clubs, laryngectomee visitors provide pre- and/or postoperative support to patients who have recently undergone removal of the larynx.

Ostomy Rehabilitation. Some patients with intestinal or urinary cancers must have abdominal ostomies (surgically constructed openings for elimination of body wastes). Trained volunteers who have experienced this same type of surgery offer help on a one-to-one basis. Cooperating with the United Ostomy Association and enterostomal therapists, patients are assisted in their physical and psychological adjustment.

Patient and Family Education Programs

The Society sponsors group and individual education programs, distributes pamphlets and booklets and provides audiovisual presentations for patients of all ages and their families to help them understand and deal with the complexities of the disease.

I Can Cope. Information is provided on cancer therapy, treatment, side effects, nutrition, resource availability and other topics of interest to cancer patients and their families.



COSTS OF CANCER

A study by the National Center for Health Statistics (NCHS) puts overall medical costs for cancer at \$71.5 billion for 1985; \$21.8 billion for direct costs; \$8.6 billion for so-called morbidity costs (cost of lost productivity), and \$41.2 billion for mortality costs. The figures show that cancer accounts for 10% of the total cost of disease in the U.S. and that its share of the total cost of premature death is about 18% of all causes of death.

Individuals have several sources of help in paying for cancer costs: third-party payers such as Blue Cross

and private insurance companies, public agencies and private health organizations. Cancer is covered by personal insurance plans either under narrowly defined cancer policies or through catastrophic illness provisions in comprehensive insurance programs.

The Third National Cancer Survey showed that for patients under 65 years, Blue Cross and private insurers were the source of payment in over 77% of the cases. For patients over 65, Medicare paid expenses in nearly 88% of the cases.

RESEARCH

THE ACS AND RESEARCH

The American Cancer Society is the largest source of private cancer research funds in the United States, second only to the National Cancer Institute, an agency of the Federal government.

The Society's overall investment in research each year has grown steadily from \$1 million in 1946 to over \$86 million* today. This sum represents nearly a third of the total ACS budget. To date, the Society has invested close to \$1 billion in cancer research.

The research program focuses primarily on investigator-initiated projects, rather than directed research undertaken on a contract basis. With the exception of staff and facilities to carry out its epidemiological studies, the ACS neither hires staff researchers nor operates its own laboratories. This gives the Society the freedom to place its grants where the most innovative and promising ideas are being explored.

A key factor in the role of the Society in cancer research is providing qualified scientists with alternative funding sources to carry out their work. The Society believes it can make the most effective use of its research funds by supporting investigators working in established medical and other scientific institutions across the country. In this way there is a minimum of overhead and a maximum of flexibility to make sure that research money has the highest probability of yielding results that will benefit people.

Applications for ACS grants are put through a rigorous process of evaluation, beginning with careful study by the appropriate one of 12 scientific review committees and then by two additional groups of experts. They must be given final approval by the

National Board of Directors.

Kinds of Grants

The Society's research program is diverse in concept and recipients. It provides support both for established scientists and those starting out on their own independent research. It funds postdoctoral training for promising young investigators and stimulates new ideas in cancer research among those working in universities, institutes and teaching hospitals.

Overall, the program offers five types of grants: (1) Research and Clinical Investigation Grants to finance investigator-initiated research; (2) Institutional Research Grants to universities, institutes and hospitals to support pilot studies and the work of young investigators in caricer; (3) Research Personnel Grants to outstanding scientists and fellows specializing or planning to specialize in cancer research; (4) Research Development Program Grants to provide rapid funding for priority projects; and (5) Special Institutional Grants for Cancer Cause and Prevention Research to provide longer term funding for interdisciplinary projects for which support is not readily available through the Society's other programs.

Research Professorships. The Research Professorship program, unique in the field, has been in existence

since 1957. The Society supports 25 of the nation's most gifted scientists for long periods of time, until their retirement. These are people devoting their lives' work to cancer research. Freed of major administrative responsibilities and other restrictions, they can concentrate on their fields of scientific investigation.

Clinical Research Professorships. This novel and unique program is a new initiative of the Society to provide support for clinicians and scientists who are able to facilitate advances in clinical cancer research by bridging the gap between basic science and clinical medicine. Three awards have been made since the inception of the program in 1987.

Physicians' Research Training Fellowships. Unique in the research world, this type of Research Personnel Grant was inaugurated in 1981 because of a dearth of MD's in the research field. It provides an opportunity for physicians to take three years from their medical careers to train as researchers.

Research Development Program. Established to identify and provide rapid funding for high priority projects, approved applications can be funded in *less than three months*. This compares with the 10 to 18 months required by the Federal government before a new application can be funded.

The kinds of research projects eligible under the Research Development Program include: (1) unique research opportunities which cannot wait for the normal lengthy funding procedures; (2) unanticipated needs relating to research already under way; (3) program coordination, especially that involving clinical trials and the dissemination of research results to community hospitals; and (4) program integration between the American Cancer Society and other health organizations.

All applications are evaluated for merit, qualifications and productivity of the investigator, relevance, need for rapid funding, and probability of the project's eventual contribution to cancer control. More than \$13 million has been appropriated so far to the Research Development Program, over half of which has been for interferon research.

Interferon Research. Interferons, a group of natural body proteins, were discovered as antiviral agents, and later found to have some anticancer activity. In 1978, the Society invested an unprecedented \$2 million to purchase interferon for clinical trials. At the time, interferons were extremely scarce and expensive, since they were obtained from human blood cells.

Interferons work dramatically to improve certain diseases such as hairy cell leukemia and some lymphomas and papillomas. In these the frequency of improvement approaches 90%. In other diseases, such as kidney cancer and Kaposi's sarcoma, there are dramatic responses, but they are far less frequent—on the order of 10-30%; in lung and colon cancer, interferon rarely causes improvement. The thrust of current research with interferons is to attempt to improve their effectiveness by combining them with

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more conventional chemotherapeutic drugs and by using mixtures of different interferons.

Large quantities of certain types of interferon can be produced now using the techniques of recombinant DNA. They are far cheaper and purer than the original human blood substances, and have recently been approved for marketing. The new technology is also extremely valuable for producing complex drugs and chemicals to benefit mankind. Furthermore, other substances, called biologic response modifiers, which use immune means to combat cancer are being developed at a rapid pace, including interleukin-2/lymphokine-activated killer cell (IL-2/LAK) reagents which appear to shrink such cancers as kidney and melanoma. Some of these reagents are very potent and quite toxic, and the search is on to find effective and safer ways to use them in patients.

Research in the 80's

In addition to ongoing interferon studies, ACS-funded researchers continue to investigate broad areas of cancer research in this decade. For example, they are exploring:

Genetic engineering. One method in this new technology, recombinant DNA, is already being used to produce interferon. It has among its potential uses the manufacture of powerful new drugs, correcting impaired immune systems, even modifying heredity by transplanting foreign genes. It is hoped that the process will yield other anticancer activities. Some that appear quite promising at the moment are tumor necrosis factor (TNF), interleukin-2, and certain bone marrow growth regulators.

Monoclonal antibodies. Tailor-made, highly specific monoclonal antibodies can be produced that will preferentially recognize cancer cells, and thus be able to detect cancer early, when the disease is most curable, before clinical signs appear. Monoclonal antibodies already have been used to deliver drugs directly to tumors, killing them but sparing healthy tissue.

Mechanisms of carcinogenesis. Investigators are approaching these key questions from many angles. One model, as found in animals, shows that cancer in humans develops in a two-step process — initiation and promotion. Other questions include: Are there proto-oncogenes, normal genes serving as master switches for early tissue development, which induce normal cells to become cancerous later in life? If so, what turns them on? Can they be programmed to stay

off? Do viruses, already known to cause cancer in animals, also cause cancer in humans, perhaps by activation of these proto-oncogenes? Conversely, a normal gene that appears to suppress cancer development has been isolated recently. Does this gene produce a substance that stops normal cells from dividing before they become cancerous? Many of these questions are now being answered.

Chemoprevention. There is strong evidence that perhaps people can be protected from cancer by what they eat or drink, or by other substances or lifestyles that serve as defense mechanisms. Clues are being pursued by ACS researchers studying such agents as vitamin A; retinoids (synthetic forms of vitamin A); vitamin C; vitamin E; the chemical element selenium, found in the soil; and other naturally occurring substances in brussels sprouts, cabbage, and certain other foodstuffs. This is a new and important area which needs further research so that recommendations can be developed on how people should change their lifestyles to reduce their chances of getting cancer.

Still other ACS investigators are looking for ways to detect cancer earlier by tracing a cell's biochemical markers. They are exploring evidence that the outbreak of the rare cancer, Kaposi's sarcoma, frequently found in patients with AIDS, is linked to a breakdown in the individual's immune system. And they are testing the hypothesis that certain chemicals enhance a tumor's responsiveness to radiation therapy.

1

The Financial Research Picture

In fiscal 1988, the ACS made 818 grants to major institutions in this country and to scientists working here and abroad. The total amount, subject to audit, was over \$83 million. This does not include some \$3 million granted directly by ACS Divisions. The following table—covering the years 1985-1988 inclusive—lists the number of applications received, the total number of dollars required, and those actually funded by the ACS National Office.*

| | Req | uested | Funded | | |
|------|--------|---------------|-------------|--------------|--|
| Year | Number | Amount | Number | Amount | |
| 1985 | 2,096 | \$273,968,261 | 712 | \$63,703,751 | |
| 1986 | 2,438 | 364,065,882 | <i>7</i> 75 | 73,896,704 | |
| 1987 | 2,385 | 368,645,879 | 810 | 77,516,363 | |
| 1988 | 2,281 | 357,408,459 | 818 | 83,936,347 | |

CANCER AND THE ENVIRONMENT

Most cancer cases in the United States are believed to be environmentally related, that is, associated in some way with our physical surroundings, personal habits or lifestyles.

Occupational hazards, although associated with only a small percentage of cancers, are under close surveillance. Virtually every suspected major chemical and other substance in the workplace presumed to be a health risk is under investigation. Each study can require years and hundreds of thousands of dollars to complete.

Some environmental causes of cancer are well known. About 30% of all cancers are directly related to the use of tobacco, either alone or in conjunction with excessive consumption of alcohol.

Other causes are harder to determine. Diet is suspected as an important element in cancer risk, some say as much as 35% of all cancer deaths. There is much research underway on the role diet and nutrition play in the development of cancer.

To help identify environmental factors in human cancer, the American Cancer Society has undertaken

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a two-part program of environmental cancer research. This involves (1) Cancer Prevention Study II, an epidemiologic study to examine the relationship of environment and lifestyle to cancer development; and (2) support of extramural cancer cause and prevention research projects.

The American Cancer Society's Cancer Prevention Study II

One of the largest research studies ever carried out in the United States was launched in 1982. Cancer Prevention Study II, a long-term prospective study, is examining the habits and exposures of more than one million Americans to learn how lifestyles and environmental factors affect the development of cancer.

Modeled after the first ACS Cancer Prevention Study (1959-72), CPS-II is similar in method but wider in scope and involves more participants.

Over 77,000 volunteers enrolled 1.2 million men and women in the study. These volunteer researchers distributed a four-page confidential questionnaire to participants who were asked about their exposures to certain environmental conditions, their history of disease and their lifestyles. The questionnaires were designed to elicit more than 500 pieces of information each, which were computerized for statistical analysis.

Many of the questions focus on health issues of current concern. These include risks of certain drugs, foods and various occupational exposures; low-tar and nicotine cigarettes; consumer products; long-term exposure to low-level radiation; and the health effects associated with air and water pollution.

For a period of six years, the volunteers will keep track of the status and whereabouts of study participants. Various suspected relationships will be tested by comparing mortality rates of differently exposed

The goal of the study is to identify those factors that increase a person's chances of developing cancer, those that carry little or no risk, and those that actually may help prevent cancer.

So far, five papers have been published from the analyses of data on the original questionnaires. One showed massive changes in American smoking habits compared to 23 years earlier in CPS I. Among men, 24% smoked, half as many as in the earlier study. More than twice as many had quit cigarette smoking. Among women, the percent who had ever smoked rose 10%, but the percent of ex-smokers quadrupled. More than one-third of male smokers and one-half of female smokers smoked brands with less than 12 mg. of tar. Another paper from CPS II showed that smoking in physicians is now down to 16%, about 14% in dentists and 23% in nurses. A third paper showed that a greater percentage of women who used artificial sweeteners gained weight over a one-year period than nonusers. An additional five papers have been completed and submitted for publication. Another paper shows that death rates from all causes were 81% higher in obese and underweight people than those of average weight and that degree of exercise was negatively correlated with cancer death rates.

Since the first study, new factors in our environment have been identified that may be related to cancer. The Society decided to initiate a second study to respond to the concerns of the public and scientific community about suspected carcinogens.

Without the use of ACS volunteers, the cost of carrying out CPS II would total more than \$100 million. With volunteers to collect the data, the study is estimated to cost only about \$9 million to complete.

CANCER'S SEVEN WARNING SIGNALS

- 1. Change in bowel or bladder habits
- 2. A sore that does not heal
- 3. Unusual bleeding or discharge
- 4. Thickening or lump in breast or elsewhere
- 5. Indigestion or difficulty in swallowing
- 6. Obvious change in wart or mole
- 7. Nagging cough or hoarseness

If you have a warning signal, see your doctor.

30-YEAR TRENDS IN AGE-ADJUSTED CANCER DEATH RATES PER 100,000 POPULATION 1953-55 to 1983-85

| SITES | SEX | 1953-55 | 1983-85 | PERCENT CHANGES | COMMENTS |
|-------------|----------|---------|---------|--------------------|---|
| ALL SITES | Male | 175.7 | 203.1 | + 16 | Steady increase mainly due to lung cancer. |
| ALL SITES | Female | 145.1 | 138.2 | - 5 | Slight decrease. |
| N + D D F D | Male | 7.2 | 6.1 | - 15 | Slight decrease in recent years. |
| BLADDER | Female | 3.1 | 1.8 | - 42 | Some fluctuations; noticeable decrease. |
| 22.44.1 | Male | 3.9 | 4.7 | + 21 | Early increase in both sexes; |
| BRAIN | Female | 2.6 | 3.2 | + 23 | later leveling off, reasons unknown. |
| | Male | 0.3 | 0.2 | ٠ | Constant rate. |
| BREAST | Female | 26.2 | 27.1 | + 3 | Slight fluctuations; overall no change. |
| COLON & | Male | 25.8 | 24.7 | • | Slight fluctuations; overall no change. |
| RECTUM | Female | 24.4 | 17.5 | - 28 | Slow, steady decrease. |
| | Male | 16.9 | 20.7 | + 22 | Slow steady increase, leveling in recent years. |
| COLON | Female | 18.3 | 15.0 | - 18 | Slow, steady decrease. |
| | Male | 8.9 | 4.0 | - 55 | Slow steady decrease. |
| RECTUM | Female | 6.1 | 2.4 | - 61 | Slow steady decrease. |
| | Male | 4.7 | 5.6 | + 19 | Some flucutations; small increase. |
| ESOPHAGUS | Female | 1.2 | 1.5 | • | Slight fluctuations; overall no change. |
| | Male | 3.6 | 4.9 | + 46 | Steady slight increase. |
| KIDNEY . | Female | 2.2 | 2.3 | • | Slight fluctuations; overall no change. |
| | Male | 2.6 | 2.7 | • | Slight fluctuations; overall no change in |
| LARYNX | Female | 0.2 | 0.5 | • | both males and females. |
| | Male | 8.2 | 8.4 | + 2 | Early increase, later leveling off and decrease. |
| LEUKEMIA | Female | 5.5 | 5.0 | - 9 | Early slight increase; later leveling off and decrease. |
| | Male | 6.2 | 4.9 | - 21 | Decreasing rapidly early; later leveling off. |
| LIVER** | Female . | 7.1 | 3.3 | - 54 | Some fluctuations; steady decrease. |
| | Male | 28.0 | 73.1 | +161 | Steady increase in both sexes due to |
| LUNG | Female | 5.1 | 25.3 | +396 | cigarette smoking. |
| | Male | 8.0 | 11.1 | +39 | Slow steady increase in |
| LYMPHOMAS | Female | 5.1 | 7.5 | +47 | both males and females. |
| 00 | Male | 6.0 | 5.2 | • | Slight fluctuations; overall no change |
| ORAL | Female | 1.5 | 1.8 | • | in both males and females. |
| OVARY | Female | 8.6 | 7.8 | - 9 | Steady increase; later leveling off and decrease. |
| | Male | 9.1 | 10.2 | + 12 | Steady increase in both sexes, then leveling off, |
| FANCREAS | female | 5.7 | . 7.2 | + 26 | reasons unknown. |
| FIRIDSTATE | Male | 21.3 | 23.2 | + 9 | Fluctuations throughout; overall slight increase. |
| | Male | 3.1 | 4.0 | + 29 | Slight fluctuations; slight increase. |
| SKIN | Female | 1.9 | 1.8 | • | Slight fluctuations; overall no change. |
| | Male | 21.3 | 10.2 | ~ 52 | Steady decrease in both sexes; reasons |
| STOMACH | Female | 11.2 | 3.5 | - 69 | unknown. |
| UTERUS | Female | 19.0 | 7.1 | - 63 | Steady decrease. |

^{*}Percent changes not listed because they are not meaningful.

^{**}Primary and non-specified.

SUMMARY OF RESEARCH GRANTS & FELLOWSHIPS AWARDED BY ACS (National Society & Divisions) DURING THE FISCAL YEAR ENDED AUGUST 31, 1988 (Subject to Audit)

| American Health Foundation, New York, NY | (1) | \$1,000,000 | Medical Research Council, Cambridge, England | (1) | \$ 70,000 | Univ. of Connecticut, Storrs | (4) | \$ 679.00 |
|--|------|------------------|--|------|-----------|--|--------|-----------|
| Arizona State Univ., Tempe, AZ | (1) | 82,000 | Michigan Cancer Fdn., Detroit | (4) | 680,500 | Univ. of Delaware, Wilmington | (1) | 63.60 |
| Baylor College of Medicine, Houston, TX | (5) | 462,000 | Michigan State Univ., East Lansing | (3) | 614,000 | Univ. of Florida, Gainesville | (3) | 311,00 |
| Beth Israel Hosp., Boston, MA | (3) | 208,500 | Miller's Children's Hospital, Long Beach, CA | (1) | 250,000 | Univ. of Georgia, Athens | (1) | 205,00 |
| Boston Univ., Boston, MA | (4) | 358,500 | Montefiore Hospital, Bronx, NY | (1) | 81,000 | Univ. of Hawaii, Honolulu | (1) | 10,00 |
| Brandeis Univ., Waltham, MA | (5) | 246,000 | Mount Sinai Sch. of Med., New York, NY | (4) | 205,500 | Univ. of Illinois, Urbana | (5) | 256,57 |
| Brigham & Women's Hosp, Boston, MA | (1) | 167,000 | Nat'l Cancer Inst., Bethesda, MD | (1) | 69,600 | Univ. of Indiana, Bloomington | (4) | 353,50 |
| Brown Univ., Providence, RI | (5) | 562,500 | Nat'l Inst. of Allergy & Infectious Disease, | | , | Univ. of Kansas, Lawrence | (3) | 189,00 |
| California Inst. of Tech., Pasadena | (10) | 707,850 | Bethesda, MD | (1) | 63,300 | Univ. of Kentucky, Lexington | (1) | 30,00 |
| California State Coll., Fullerton | (1) | 10,000 | Nat'l Insts. of Health, Bethesda, MD | (1) | 69,000 | Univ. of Louisville, Louisville, KY | (1) | 85,00 |
| Carnegie Inst. of Washington, Baltimore, MD | (3) | 119,500 | Nat'l Jewish Hosp. & Res. Ctr., Denver, CO | (5) | 705,318 | Univ. of Maryland, Baltimore | (5) | 790,00 |
| Carnegie-Mellon Univ., Pittsburgh, PA | (1) | 160,000 | New England Med. Ctr. Hosp., Boston, MA | (1) | 80,000 | Univ. of Massachusetts, Amherst | (1) | 110,00 |
| Catholic Med. Ctr. of Brooklyn & Queens, NY | (1) | 96,000 | New York Acad. of Sciences, New York, NY | ίij | 10,000 | Univ. of Med. & Dentistry of NJ, Newark, NJ | (5) | 572,00 |
| Case Western Reserve Univ., Cleveland, OH | (3) | 343,812 | New York Medical Center, Valhalla | ίij | 175,000 | Univ. of Miami, Coral Gables, Fl. | (3) | 447.00 |
| Children's Hospital of San Francisco, CA | (1) | 200,000 | New York Univ., New York, NY | (9) | 1,710,694 | Univ. of Michigan, Ann Arbor | (10) | 1,167,72 |
| City Coll. of City Univ. of New York | ίij | 79,000 | North Carolina State Univ., Raleigh | (1) | 68,000 | Univ. of Minnesota, Minneapolis | (9) | 1,023,00 |
| City of Hope Nat'l Med. Ctr., Duarte, CA | ίij | 131,000 | Northwestern Univ., Chicago, IL | (7) | 603,920 | Univ. of Nebraska, Omaha | (5) | 1,264,82 |
| Cold Spring Harbor Lab., Cold Spring Hbr, NY | (6) | 306,500 | Northern California Ca. Program, Oakland | (1) | 193,000 | Univ. of New Hampshire, | (1) | |
| Columbia Univ., New York, NY | (15) | 1,398,400 | | (i) | 103,000 | Univ. of New Mexico, Albuquerque | | 160,00 |
| Cornell Univ., Ithaca, NY | (3) | 354,000 | Oak Ridge Nat'l Lab., Oak Ridge, TN | | 277,000 | Univ. of North Carolina, Chapel Hill | (3) | 440,00 |
| Cornell Univ., New York, NY | (3) | | Ohio State Univ., Columbus | (4) | 210,000 | Univ. of North Carolina, Chaper Hill Univ. of North Dakota, Grand Forks | (10) | 1,137,92 |
| | • .• | 357,600 | Oregon Health Sciences Lab., Portland | (2) | | | (1) | 102,00 |
| Creighton Univ., Omaha, NE | (1) | 94,000 | Oregon State Coll., Sci. Res. Inst., Corvallis | (3) | 134,987 | Univ. of Oregon, Eugene | (4) | 305,00 |
| Dana-Farber Cancer Ctr., Boston, MA | (14) | 1,097,500 | Oregon State Univ., Corvallis | (1) | 32,000 | Univ. of Pennsylvania, Philadelphia | (8) | 928,64 |
| Dartmouth Coll., Hanover, NH | (3) | 368,875 | Oxford University, England | (2) | 140,100 | Univ. of Pittsburgh, Pittsburgh, PA | (8) | 1,290,00 |
| Drexel Inst. of Tech., Philadelphia, PA | (2) | 320,000 | Pacific Northwest Res. Fdn., Seattle, WA | (1) | 110,000 | Univ. of Rochester, Rochester, NY | (8) | 1,060,43 |
| Duke Univ., Durham, NC | (10) | 998,855 | Pennsylvania State Univ., Hershey | (7) | 501,000 | Univ. of Rhode Island, Kingston | (1) | 43,20 |
| Duquesne Univ., Pittsburgh, PA | (1) | 70,000 | Portland State Univ., OR | (1) | 174,000 | Univ. of South Carolina, Columbia | (2) | 83,00 |
| East Carolina Univ., Greenville, NC | (2) | 241,500 | Princeton Univ., Princeton, NJ | (15) | 1,327,513 | Univ. of Southern California, Los Angeles | (5) | 578,77 |
| Emory Univ., Atlanta, GA | (3) | 560,000 | Pub, Health Res. Inst., New York, NY | (3) | 497,000 | Univ. of South Florida, Tampa | (2) | 308,00 |
| Eleanor Roosevelt Inst. for Ca. Res., Denver, CO | (2) | 70,000 | Purdue Univ., Lafayette, IN | (3) | 293,000 | Univ. of Tennessee, Memphis | (4) | 408,00 |
| Foundation for Biomedical Res., Washington, DC | (1) | 10,000 | Reed Coll., Portland, OR | (1) | 127,000 | Univ. of Texas (Various Locations) | (28) | 3,044,20 |
| Fred Hutchinson Cancer Res. Ctr., Seattle, WA | (2) | 283,000 | Rockefeller Univ., New York, NY | (7) | 975,625 | Univ. of Toledo, Toledo, OH | (1) | 63,00 |
| Georgetown Univ., Washington, DC | (1) | 101,000 | Roswell Park Mem. Inst., Buffalo, NY | (13) | 1,519,449 | Univ. of Utah, Salt Lake City | (4) | 600,00 |
| Hahnemann Med. Coll., Philadelphia, PA | (2) | 63,000 | Rutgers Univ., New Brunswick, NJ | (1) | 160,000 | Univ. of Vermont, Burlington | (2) | 288,00 |
| Harvard Medical School, Cambridge, MA | (19) | 1,391,703 | St. Jude Children's Res. Hosp., Memphis, TN | (5) | 646,000 | Univ. of Virginia, Charlottesville | (9) | 865,00 |
| Harvard Sch. of Pub. Health, Boston, MA | (3) | 300,000 | St. Louis Univ., St. Louis, MO | (1) | 40,000 | Univ. of Washington, Seattle | (10) | 1,085,31 |
| Henry Ford Hospital, Detroit, MI | (1) | 98,000 | Salk Inst. for Biological Studies, San Diego, CA | (2) | 85,000 | Univ. of Wisconsin, Madison | (11) | 778,72 |
| Inst. for Cancer Res., Philadelphia, PA | (3) | 203,000 | Scripps Clinic Res. Fdn., La Jolla, CA | (3) | 393,000 | Univ. of Wyoming, Laramie | (1) | 20,00 |
| Illinois Cancer Council, Chicago, IL | (1) | 100,000 | Showa Univ. Res. Inst., St. Petersburg, FL | (1) | 70,000 | Univ. Louis Pasteur, Strasbourg, France | (1) | 70,00 |
| Jackson Lab., Bar Harbor, ME | (3) | 196,250 | Sloan-Kettering Inst., New York, NY | (30) | 3,426,000 | Vanderbilt Univ., Nashville, TN | (5) | 455,22 |
| Jefferson Medical Coll., Philadelphia, PA | (1) | 18,550 | Stanford Univ., Stanford, CA | (21) | 1,619,400 | Virginia Mason Hospital, Seattle, WA | (1) | 105,50 |
| Jewish Hospital of St. Louis, MO | ίń | 208,000 | State Univ. of Iowa, Iowa City | (3) | 300,500 | Virginia Polytechnic Inst., Blacksburg | (i) | 115,00 |
| Johns Hopkins Univ., Baltimore, MD | (19) | 2,011,000 | State Univ. of NY, Albany | (1) | 25,797 | Wake Forest Coll., Bowman Gray Sch. of Med., | , | 113,00 |
| Kaiser Foundation Res. Inst., CA | (1) | 45,838 | State Univ. of NY, Buffalo | (i) | 200,000 | Winston-Salem, NC | (5) | 427,00 |
| Kansas State Univ., Manhattan | (3) | 215,285 | State Univ. of NY, Downstate | (1) | 151,000 | | (1) | 35,00 |
| Kirksville Coll. of Osteopathic Med., MO | (1) | 84,000 | State Univ. of NY, Stony Brook | (9) | | Washington State Univ., Pullman | | 731,00 |
| | | 84,000 84,000 | Syracuse Univ., Syracuse, NY | | 631,695 | Washington Univ., St. Louis, MO | (7) | |
| La Jolla Cancer Res. Ctr., La Jolla, CA | (1) | | | (3) | 223,500 | Wayne State Univ., Detroit, MI | (3) | 161,00 |
| Lehigh Univ., Bethlehem, PA | (2) | 140,000 | Temple Univ., Philadelphia, PA | (2) | 218,000 | Whitehead Inst., Cambridge, MA | (10) | 639,52 |
| Louisiana State Univ., Baton Rouge | (4) | 503,000 | Texas A&M, College Station | (1) | 90,500 | Wistar Inst., Philadelphia, PA | (9) | 1,291,00 |
| Loyola University, Chicago, IL | (1) | 160,000 | Tufts-New England Med. Ctr., Boston, MA | (1) | 90,500 | Worcester Fdn. for Exptl, Bio., Shrewsbury, MA | (1) | 98,00 |
| M.D. Anderson Cancer Ctr., Houston, TX | (1) | 200,000 | Tufts Univ., Medford, MA | (3) | 285,500 | Woods Hole Ocean. Inst., Woods Hole, MA | (1) | 180,00 |
| Marine Biology Lab., Woods Hole, MA | (1) | 10,000 | Tulane Univ., New Orleans, LA | (2) | 138,000 | Wright State Univ., Dayton, OH | (1) | 149,00 |
| Massachusetts Eye, Ear Infirmary, Boston | (7) | 87,406 | Univ. of Alabama Med. Ctr., Birmingham | (9) | 953,008 | Yale Univ., New Haven, CT | (19) | 1,716,22 |
| Massachusetts General Hosp., Boston | (3) | 329,500 | Univ. of Arizona, Tucson | (2) | 64,800 | Yeshiva Univ.—Albert Einstein, The Bronx, NY | (17) | 1,785,00 |
| Massachusetts Inst. of Technology, Cambridge | (16) | 1,015,150 | Univ. of Arkansas, Fayetteville- | (1) | 40,000 | | (0.40) | en 026 24 |
| Medical Biology Institute, La Jolfa, CA | (4) | 536,000 | Univ. of Calif. (Various Locations) | (95) | 9,544,063 | SUBTOTAL | (818) | 83,936,34 |
| Medical Coll. of Pennsylvania, Philadelphia | (1) | 108,000 | Univ. of Chicago, Chicago, IL | (13) | 1,182,787 | Division Research Grants | (1) | 3,000,00 |
| Medical Coll. of Virginia, Richmond | (3) | 325,000 | Univ. of Cincinnati, Cincinnati, OH | (3) | 300,000 | | | • • |
| | (4) | 477,000 | Univ. of Colorado, Boulder | (14) | 1,407,400 | . TOTAL | (910) | 86,936,34 |

Note: Numbers in parentheses indicate number of grants per institution for the year ended August 31 1988; totals subject to audit.

COMPREHENSIVE CANCER CENTERS

The institutions listed have been recognized as Comprehensive Cancer Centers by the National Cancer Institute. These centers have met rigorous criteria imposed by the National Cancer Advisory Board. They

receive financial support from the National Cancer Institute, the American Cancer Society and many other sources.

ALABAMI

University of Alabama Comprehensive Cancer Center 1918 University Boulevard, Room 108 Birmingham, Alabama 35294 Phone: (205) 934-6612

CALIFORNIA.

University of Southern California Comprehensive Cancer Center Kenneth Norris, Jr. Hospital & Research Institute 1441 Eastlake Avenue Los Angeles, California 90033-0804 Phone: (213) 226-2370

Jonsson Comprehensive Cancer Center 10-247 Factor Building 10833 Le Conte Avenue Los Angeles, (California 90033 Phone: (213) 825-8727

CONNECTICUT

Yale University Comprehensive Cancer Center 333 Cedar Street New Haven, Connecticut 06510 Phone: (203) 785-6338

DISTRICT OF COLUMBIA Howard University

Comprehensive Cancer Center 2041 Georgia Avenue, N.W. Washington, D.C. 20060 Phone: (202) 636-7610 or 636-5665

Vincent T. Lombardi Cancer Research Center Georgetown University Medical Center 3800 Reservoir Road, N.W. Washington, D.C. 20007 Phone: (202) 687-2110

FLORIDA

Papanicolaou Comprehensive Cancer Center University of Miami Medical School 1475 N.W. 12th Avenue Miami, Florida 33136 Phone: (305) 548-4850

ILLINOIS

Illinois Cancer Council 36 South Wabash Avenue Chicago, Illinois 60603 Phone: (312) 226-2371

University of Chicago Cancer Research Center 5841 South Maryland Avenue Chicago, Illinois 60637 Phone: (312) 702-6180

MARYLAND

The Johns Hopkins Oncology Center 600 North Wolfe Street Baltimore, Maryland 21205 Phone: (301) 955-8638

MASSACHUSETTS

Dana-Farber Cancer Institute 44 Binney Street Boston, Massachusetts 02115 Phone: (617) 732-3214

MICHIGAN

Meyer L. Prentis Comprehensive Cancer
Center of Metropolitan Detroit
110 East Warren Avenue
Detroit, Michigan 48201
Phone: (313) 833-0710, ext. 429

MINNESOTA

Mayo Comprehensive Cancer Center 200 First Street, S.W. Rochester, Minnesota 55905 Phone: (507) 284-3413

NEW YORK

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News & Comment

SCIENCE, Vol. 253, No. 5022, pages 842 - 844 (23 August 1991).

Get-the-Lead-Out Guru Challenged

 $A\ decade\ old\ scientific\ argument\ over\ the\ effects\ of\ low\ -level\ lead\ on\ IQ\ turns\ nasty\ following\ allegations\ of\ misconduct$

As AN ENVIRONMENTAL BOGEYMAN, LEAD'S hard to beat. It ranks right up there with asbestos, dioxin, and nuclear waste. Vice President Dan Quayle has even suggested that lead in the drinking water at the vice presidential mansion might have caused the Bushes' bouts with Graves' disease.

But, irrational fears aside, there's no question that high lead levels can cause brain damage—it's only at low levels of exposure that there is still a debate about what amount of lead in the blood can cause detectable behavioral and medical problems. And that debate has been tainted by a festering, 10year-old dispute over the credibility of data published by Herbert Needleman of the University of Pittsburg, a world-renowned researcher on lead toxicity and leading adviser to the government on lead issues. Now, in the wake of a government lawsuit against the owners of a lead smelter in which Needleman was to have testified—but never did because the case was settled out of court—his critics have filed a complaint with federal investigators alleging that Needleman engaged in scientific misconduct a decade ago. They accuse the government of helping cover up the flaws in his research in order to deflect criticism of its policy decisions.

To Needleman, the charges are nothing more than old mud slung with new vigor—thoroughly debunked criticisms kept alive by a lead industry desperate to discredit his research.

Regardless of who is right, the Needleman saga shows how hard it is to put to rest charges from persistent critics, or, conversely, to prove misconduct against an acknowledged leader in a scientific field. But it also raises additional questions, widely applicable to other scientific disputes, about who should have access to data collected with federal support. And, of course, it refocuses attention on a matter that is especially meaningful to a lot of parents: Just how strong is the link between low-level lead exposure and intelligence deficits?

The story begins with a paper by Needleman and his colleagues in the 29 March 1979 issue of *The New England Journal of Medicine* showing that schoolchildren with what all would agree were "high," but

not actually toxic, lead levels did significantly poorer in the classroom and had measurably lower IQs than those with "low" lead levels. In order to get a clearer picture of exposure, the researchers had looked at lead concentrations in the children's baby teeth, as well as the more labile measure of lead in the blood. Suzanne Binder, chief of the Lead Poisoning Prevention Branch at the Centers for Disease Control (CDC) in Atlanta, says that most people's first reaction to Needleman's study was "so what?" since the drop in IQ was only 3 or 4 points. But Binder says policymakers came to realize that even a small drop would be important if it was affecting millions of children.

Two years after the *Journal* article appeared, Claire Ernhart, a psychologist now at

crude measure like IQ, except at some of the highest levels of exposure, just below what would be considered toxic.

The appearance of the *Pediatrics* article touched off what has been a decade-long personal feud between Ernhart and Needleman. They have squared off at numerous scientific meetings with a vigor that has left observers shaking their heads. "Personal hostility is putting it mildly," says Binder.

But the Needleman/Ernhart squabble might have remained nothing more than a classic confrontation between scientists with starkly opposing views had it not entered, in 1983, into a new and grander forum. The year before, the Environmental Protection Agency (EPA) had begun a major review of national air-quality standards for lead and

wanted to review all recent data on the [≅] health effects of lead exposures. In an effort "to resolve major points of controversy concerning some of the most important and controversial" studies, Lester Grant, director of the EPA's environmental criteria and assessment office, convened a special panel to look into both Needleman's and Ernhart's work (Science, 25 November 1983, p. 906).



Clearing the air. Herbert Needleman says the lead industry is behind attempts to discredit his research.

Case Western Reserve University, and her colleagues fired the first shot across Needleman's bow. Writing in the journal Pediatrics, they suggested that there were serious methodological flaws in the Needleman paper. Ernhart argued that Needleman had not done an adequate job of controlling for confounding variables—other factors such as poor schools or parental neglect that might explain the difference in IQ scores—and had performed so many comparisons that he was bound to come up with a few that were statistically significant merely by chance. Ernhart's own work suggested that most lead effects were too small to be detected by a

The panel traveled

to Needleman's lab, examined some of his data, and decided there were several problems with the study. Specifically, the panel members concluded that Needleman had used inappropriate measures to categorize lead exposure and had not provided sufficient justification for excluding subjects, with from the study. Moreover, they expressed concern about missing data, and some of the statistical analyses Needleman had employed, all of which led them to conclude that the study results "neither support nor refute the hypothesis that low or moderate levels of [lead] exposure lead to cognitive or behavioral impairments in children." The

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panel reached the same conclusion about two of Ernhart's papers, which they also criticized for methodological flaws.

While Ernhart took the panel's rebuke quietly, Needleman fought back. He insisted that the panel's conclusions were flawed, and he wrote a spirited, point-by-point refutation of the criticisms levied at his work. He blasted Grant for printing the report before sending it to him for review, accusing him of violating an agreement he said he and Grant had made. Needleman

"It was really the data analysis strategy that I looked at, and that to me [was] outrageous."

-Sandra W. Scarr

also performed some new analyses of his original data, and by the time the panel's report was presented to the EPA advisory panel that would decide on the new lead standards, both Grant and the advisory panel had made a 180-degree turn. Now they were convinced that Needleman's original conclusions were accurate. Indeed, those conclusions subsequently became part of the scientific basis for the revised air lead standards EPA promulgated in 1986.

But Ernhart was not daunted by this setback; she continued to criticize Needleman's work. And her willingness to argue that the link between low-level lead exposure and behavioral problems was being overstated won favor with the lead industry. As early as 1982, she had agreed to testify in favor of the industry's position before an EPA panel contemplating phasing out all leaded gasoline. Just last year she wrote to Senator Harry Reid (D-NV) telling him that basing legislative action on Needleman's findings would be an "egregious error....Serious problems in the Needleman work have long been noted by scientists working in this field." And she appeared from time to time as an expert witness in cases involving lead contamination and cleanup, which brought her feud with Needleman into a new arena: the courtroom.

Their latest faceoff—which has escalated beyond the hazards of lead to the high-stakes "game" of scientific fraud and misconduct charges—began in 1990 with a Superfund case brought by the government against Sharon Steel, UV Industries, and Atlantic Richfield Company. Over a period of several decades, each company had had a financial interest in a defunct lead smelter in

Midvale, Utah. The government case sought money for the cleanup of some 250 acres of tailings from a milling facility that prepared the lead ore for the smelter. The government intended to show that the tailings posed a health risk to children living in the area and hired none other than Herbert Needleman as an expert witness to testify to the dangers the tailings posed.

For their part, the corporations' lawyers turned to Ernhart as an expert witness. In addition, the defense team brought in



University of Virginia psychologist Sandra Wood Scarr, whose work focuses on factors affecting children's educational development. She had also served as a member of the EPA panel that had

examined Needleman and Ernhart's research back in 1983. Although Scarr had been among the most critical of Needleman's work then, she says she paid no fur-

ther attention to it after the panel had wrapped up its business. Now, she and Ernhart felt that they could damage the government's case by demonstrating what they had long believed: that Needleman's



1979 paper—which they say has been "highly influential in the establishment of regulatory policies"—was seriously flawed.

They asked to see Needleman's raw data for the 1979 study. He agreed to release some of the unpublished material, but not the tapes containing his raw data. Needleman argued, in an affidavit dated 27 July 1990 that, in part because he was in the throes of moving his lab, "it would be a substantial hardship for me to find the proper data tape for this 11-year-old study." He added that since the study had been peer reviewed and the data examined by the EPA, there had already been adequate opportunity to establish the legitimacy of his results.

Needleman did say in his affidavit, however, that he would be willing to let "any scientist who wishes to examine the complete printouts of the raw data from the study come to my laboratory in Pittsburgh for as long as he or she wants." So on 20 September last year, Scarr and Ernhart, along with defense lawyers in the lead smelter case, traveled to Pittsburgh to take Needleman up on his offer. When they arrived, they were directed by Justice Department attorney W. Be jamin Fisherow, who was acting for the government, to a bare room where they were given six volumes of computer printouts containing Needleman's initial analyses of his data. Scarr and Ernhart began plowing through the analyses, although they were hampered by the fact that the data were coded, and they were given an incomplete key. Needleman himself would not talk to them.

For his part, Needleman steadfastly insists that he will happily share his data with anyone who has a legitimate interest and will answer any questions he is asked. But, he says, "I'm just not going to make it easy for people who are going to harass me," a category to which he assigns Scarr and Ernhart.

Since Scarr and Ernhart weren't able to get through all the computer printouts in one day, they returned to the lab the next morning. But this time, Fisherow asked them to sign a document saying they would

"Serious problems in the Needleman work have long been noted by scientists working in this field."

-Claire B. Ernhart

treat all the data they were being shown in absolute confidence and would discuss it only in oral testimony before the court. While such agreements are not uncommon for litigation involving private corporations, Scarr and Ernhart were appalled at what they saw as an attempt to gag them, and they refused to sign. After a few hours, lawyers for both sides decided that the visit would have to end, so Scarr and Ernhart gathered their notes and left.

Scarr says that even with only one day to study the analyses, she felt she had a clear idea of what had happened back in 1979. "It was really the data analysis strategy that I looked at, and that to me [was] outrageous." According to Scarr, the printouts show that Needleman's first set of analyses failed to show a relationship between lead level and subsequent intelligence tests. "Not one sing variable came out as statistically different between the top 10% [of lead-exposed children]

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and the bottom 10% of the sample," she says. It was only by rerunning the analyses, eliminating important variables that might also causes changes in IQ scores, that "he got results he wanted."

Scarr's harsh view of Needleman might never have become public, however, had it not been for a curious legal twist-one with potentially major ramifications for the availability of government research data. Before Scarr and Ernhart had a chance to present their conclusions about Needleman and his data in the Utah court case, the litigants settled the case. The defendants agreed to pay the government \$63 million—the cost of cleaning up the lead tailings. Losing the chance to put the charges on record in open court, Scarr and Ernhart wrote a report that they planned to send to the National Institutes of Health (NIH) Office of Scientific Integrity (OSI), since Needleman's study had been funded with NIH money. But 4 days before the settlement agreement was announced, the government lawyers took a remarkable step: They asked the court to force Scarr and Ernham to return their notes on the Needleman data and refrain from speaking about what they had found-essentially the same rules Scarr and Ernhart refused to agree to back in Pittsburgh when they were poring over Needleman's printouts.

Scarr and Ernhart immediately conded—and believe today—that the govinment was trying to protect Needleman because his research forms the backbone of government lead policy.

Government lawyer Fisherow will not say explicitly why the government sought to gag Scarr and Ernhart, but Needleman's affidavit gives a rationale: "Releasing these raw data to the defendants here will mean that the industry will have the capacity, if it so chooses, to manipulate this data as it sees fit. While any credible researcher should be willing to have the accuracy of his published results debated, the standards of conduct in the scientific community do not extend to making raw data available to advocates of opposing views who then are presented with the opportunity to misuse them."

Scarr and Ernhart weren't buying that argument. They hired David F. Geneson of the Washington, D.C., legal firm Hunton & Williams to fight the gag order. Geneson contended to the court that the government's request was an abridgement of Scarr and Ernhart's First Amendment rights, and that there was no good cause to suppress data that had been gathered with public money.

This argument certainly rings true with wyers who specialize in misconduct issues. It's hard to imagine a legitimate basis for the federal government asking for data to be buried," says one such attorney, Barbara

Mishkin of the Washington, D.C., firm of Hogan and Hartson.

Needleman, however, has been trying to make just such an argument by saying that the lead industry has tried to twist his data to make it appear to prove things it doesn't actually prove. Mishkin isn't impressed. "The cigarette industry is always putting out its own dubious analysis of data. Nobody pays any attention to it."

On 26 April this year, federal district court judge Bruce S. Jenkins agreed with Mishkin's point, writing that "there is something inherently distasteful and unseemly in secreting either the fruits or seeds of scientific endeavors." And that freed Scarr and Ernhart to tell their doubts about Needle-

"I just do not want to... spend the rest of my life responding to trivia. My reputation is secure."

-Herbert L. Needleman

man and his data to anyone they chose. Their first step was to write a report based on their day-and-a-half visit to Needleman's lab, and they have sent a copy to the OSI. OSI officials are considering whether Needleman's actions fall under their jurisdiction, or whether Scarr and Ernhart's analyses fall under the rubric of legitimate scientific difference of opinion. Jane Duffield, a spokeswoman for the University of Pittsburgh, where Needleman did his work, says OSI has not contacted the university concerning any investigation and adds that "we're not investigating Dr. Needleman and we stand behind his work."

From Needleman's point of view, this latest round of charges is nothing more than harassment from the lead industry. "I just do not want to ... spend the rest of my life responding to trivia," he says. "My reputation is secure at least among people whom I count as important. I'm a forward looking person, and I have much more important questions to answer." And indeed, Needleman has supporters inside and outside the EPA who have seen his data and find nothing to be suspicious of. Frequent co-author David Bellinger, a psychologist and epidemiologist at Harvard University, says there is no substance to Scarr's charge that Needleman eliminated variables from his analyses until he got the results he wanted. "I've worked with the data set, and nothing has ever come to light to make me concerned

about that issue." Adds former EPA panel member Larry Kupper, a biostatistician at the University of North Carolina, Chapel Hill, "I never thought there was any misconduct."

Meanwhile, Ernhart vociferously defends herself against Needleman's charges that she is merely serving the lead industry in its attack on him. Yes, she accepts research support from the International Lead Zinc Research Organization, she admits, but says that hasn't affected her objectivity. Her objections to Needleman's conclusions began, she argues, long before she received any lead industry money. Scarr, too, bristles at the suggestion that her objectivity is tainted. "I have no ties to the lead industry," she says. "I don't care what happens to them." What bothers Scarr is that policy decisions are being made based on what she is convinced is flawed work that no one wants to take the time to examine closely. "There's just something wrong about the procedure here, and the role that science is playing in this."

Not so, says EPA's Grant. "The particular studies that are at issue there, and the publications that they are fighting about, are more or less passé," he maintains. "We now have a decade of additional research that confirms lead effects on IQ and behavioral development at much lower levels than the ones they were talking about."

But even this point of view is contested by some. Sanford L. Weiner, a political scientist based in Boston who works for the Milbank Memorial Fund, says he, like Ernhart and Scarr, believes policy actions have outpaced the science. Weiner says it is hard to find a study that clearly demonstrates adverse health effects from lead levels below 25 micrograms per deciliter of blood, the point that the CDC currently uses as its cutoff for lead poisoning. Indeed, agrees Marjorie Smith, a psychologist at the Institute for Child Health at the University of London who directed a lead study in England, 10 micrograms per deciliter—the level to which EPA wants to reduce the lead standard—is "unrealistically low" and would "cause unnecessary anxieties for parents."

Binder says that it is extremely hard to find people who don't have strong opinions about lead in the environment. "Either they're working on this because they consider it to be an incredible problem, and it's worth devoting their life to, or they think everybody else is an idiot, and they have to prove that everyone else is wrong."

So will the day come when both sides can reach a consensus? Not likely, says Binder: "They will all go to their graves thinking the other side is made up of total idiots."

■ JOSEPH PALCA

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Letter to the New England Journal of Medicine [September, 1990]

To the Editors: In their January 11 article Needleman et al. ¹ report strikingly large effects of low lead levels on several late adolescence outcomes. For example, an estimated 7.4-fold increased odds of school failure was attributed to childhood lead dentin levels above 20 ppm. Such massive effects sizes contrast sharply with results of other studies relating low lead level to earlier developmental outcomes ²⁻⁴. The authors argue that the estimated effects represent causal relationships because their analysis controlled for ten sociodemographic covariates. This conclusion of causality may be premature, however, because the covariate set did not include measures of the quality of child care (i.e., parental responsitivity, involvement with the child, provision of books, suitable playthings, etc.), a primary confounder in previous studies of developmental lead effects. Thus the reported lead effects may be partly due to spurious association induced by variations in the caretaking environment.

Indices of child care quality such as the HOME ⁵ and the CLL ⁶ have repeatedly been found to be strongly related to lead level in poor and working class children ^{2,4,7,8}. Quality of child care is also strongly associated with developmental outcome ⁹, including school performance through adolescence ¹⁰. These confounding effects are conceptually distinct from and only partly accounted for empirically by socio-demographic variables such as maternal IQ and parental education ¹¹, which were included as covariates by Needleman et al. The fact that none of the reported lead effects were attenuated by inclusion of their covariates, as is usually the case in observational studies of low lead levels, indicates that confounders such as child care may not have been fully controlled.

On another matter, the present report is a follow-up of a 1979 report ¹² which troubled reviewers ¹³, in part, because many cases were excluded after testing. In a written response to the review ¹⁴, Needleman reported data indicating that a key IQ analysis was substantially affected by 16 of the

excluded children with excess lead, or plumbism: Prior to exclusion, with N = 187, the lead effect \underline{t} = -1.51 (\underline{p} = .133, 2 - sided); after exclusion, with N = 171, \underline{t} = -2.56 (\underline{p} = .011). This suggests the presence of high IQ's in the plumbism group. In the present follow-up report, the previously excluded cases who agreed to participate were incorporated in the analysis, including, in separate descriptive summaries, ten of the plumbism cases. Five of these plumbism cases had reading disabilities, and three out of seven failed to graduate high school. These high proportions of adverse outcomes seem to corroborate the hypothesized lead effect. However, in view of the apparently contradictory IQ data described above, a summary of the IQ scores of all 16 plumbism cases would be helpful in assessing the implications of the findings.

Claire B Ernhaut

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References

- Needleman HL, Schell A, Bellinger D, Leviton A, Allred EN. The long term effects of exposure to low doses of lead in childhood. N Eng J Med 1990;322: 83-8.
- 2. McMichael AJ, Baghurst PA, Wigg NR, Vimpani GV, Robertson EF, Roberts RJ. Port Pirie cohort study: Environmental exposure to lead and children's abilities at the age of four years. N Eng J Med 1988;319: 468-75.
- 3. Fergusson DM, Fergusson JE, Horwood LJ, Kinzett NG. A longitudinal study of dentine lead levels, intelligence, school performance and behaviour II. Dentine lead and cognitive ability. J Child Psychol Psychiatry 1988;29:793-809.
- 4. Ernhart CB, Morrow-Tlucak M, Wolf AW, Super D, Drotar D. Low level lead exposure in the prenatal and early preschool periods: Intelligence prior to school entry. Neurotoxicol Teratol 1989;11: 161-170.
- 5. Caldwell BM, Bradley R. Home Observation for the Measurement of the Environment. Unpublished manuscript. Little Rock: Univ of Arkansas at Little Rock, 1984.
- 6. Polansky NA, Borgman RD, De Saix C. Roots of Futility. San Francisco: Jossey-Bass, 1972.
- 7. Dietrich KN, Krafft KM, Pearson DT, Harris LC, Bornschein RL, Hammond PB, Succop PA. Contribution of social and developmental factors to lead exposure during the first year of life. Pediatrics 1985;75:1114-9.

- 8. Hunt TJ, Hepner R, Seaton KW. Childhood lead poisoning and inadequate child care. Am J Dis Child 1982;136:538-542.
- 9. Bradley RH, Caldwell BM, Rock SL, Ramey CT, Barnard KE, Gray C,
 Hammond MA, Mitchell S, Gottfried AW, Siegel L, Johnson DL. Home
 environment and cognitive development in the first 3 years of life: A
 collaborative study involving six sites and three ethnic groups in
 North America. Dev Psychol 1989;25:217-35.
- 10. Hess RD, Holloway SD. Family and school as educational institutions.

 In: Parke RD, ed. The Family. Chicago: Univ. Chicago Press, 1984.
- 11. Schroeder SR, Hawk B. Psycho-social factors, lead exposure and IQ. In: SR Schroeder (Ed.) Toxic Substances and Mental Retardation: Neurobehavioral Toxicology and Teratology. Washington, D.C.: AAMD Monograph Series, 1987
- 12. Needleman HL, Gunnoe C, Leviton A, Reed R, Peresie H, Maher C, Barrett P. (1979). Deficits in psychological and classroom performance in children with elevated dentine lead levels. N Eng J Med 1979;300: 689-95.
- 13. US Environmental Protection Agency. Independent peer review of selected studies concerning neurobehavioral effect of lead exposures in nominally asymptomatic children: Official report of findings and recommendations of an interdisciplinary expert review committee. (EPA-600/8-83-028A).
- 14. Needleman HL. Appendix to the ECAO critique. Unpublished manuscript, on file with the Environmental Protection Agency, 1984.

CONTROVERSIES IN BASIC SCIENCE

The Question of Thresholds for Radiation and Chemical Carcinogenesis

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INTRODUCTION

Selection of the dose-incidence model that is appropriate for predicting the risks of cancer from low-level exposure to a given carcinogen is among the most contentious issues in public health. Although the existence of a threshold in the dose-effect relationship is well documented for many, if not most, types of toxicological effects, the existence of a threshold for the mutagenic effects of ionizing radiation (1-3) and of certain chemicals (4,5) has been questioned since the middle of the century. More recently, the existence of a threshold for carcinogenic effects also has been seriously questioned, since carcinogenesis may, likewise, be envisioned to result from effects on individual cells rather than groups of cells (6-8).

Because in principle it is not possible to prove or disprove the existence of a threshold for carcinogenesis, the argument for or against the threshold hypothesis must be based on theoretical as well as empirical evidence (7,8). Some of the cogent data and concepts are surveyed in the following.

BIOLOGY OF CARCINOGENESIS

Monoclonal, Multicausal, Multistage Nature of Cancer

The evidence that cancer usually originates from a single transformed cell (9-11) implies that appropriate damage to one cell alone may suffice to increase the probability of neoplasia in a suitably susceptible individual. A single alteration, however, apparently does not suffice to convert a normal cell into a cancer cell. On the contrary, cancer typically appears to evolve through a succession of stages; for example, initiation, promotion, and progression (12,13).

The mechanism of *initiation* remains to be established, but some type of mutational change is implicated by evidence that: (i) the initiating event is relatively prompt and irreversible (14,15); (ii) most ultimate carcinogens are mutagens (16); (iii) the frequency of cell transformation that is induced by a given carcinogen is usually maximal if exposure to the agent occurs just before or during

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DNA synthesis (17); (iv) the carcinogenic potency of an initiating chemical is generally correlated with the extent to which it binds covalently to DNA and with the nature of the resulting DNA adducts; and (v) DNA to which a chemical carcinogen is bound can serve as a template for DNA replication (18) which, along with subsequent cell division, is necessary to "fix" the potential for neoplastic change (19); (vi) susceptibility to cancer is increased in persons who are deficient in their capacity to repair DNA damage (20). Whatever the nature of the mutational change may be, it results in a frequency of initiation that is orders of magnitude higher than the rate of mutations at any given gene locus (21,22), implying that multiple oncogenic sites, damage to the genome at sites unlikely to be repaired (e.g., tandem repeats), or genetic damage other than point mutations are likely to be involved (14).

The specific genes that are affected may be presumed to include antioncogenes as well as oncogenes (Table 1). Initiation can thus be envisioned to result either from the homozygous inactivation or deletion of an antioncogene, or from the aberrant activation of an otherwise normal proto-oncogene, through aneuploidy, chromosomal rearrangement, or point mutation. For neoplastic transformation, as opposed to initiation, the activation of a single oncogene alone appears to be insufficient (13).

Although initiation can result from only one exposure to an appropriate initiating agent, tumor promotion typically requires repeated and sustained exposures to an appropriate promoting agent, although low doses of the agent may suffice. In two-stage mouse skin carcinogenesis, for example, nanomolar concentrations of 12-O-tetradecanoyl phorbol-13-acetate (TPA) are sufficient to

Table 1

Comparative Properties of Oncogenes and Antioncogenes

| Oncogenes | Antioncogenes | | | |
|------------------------------------|---|--|--|--|
| Gene active | Gene inactive | | | |
| Specific translocations | Deletions or invisible mutations | | | |
| Translocations not hereditary | Mutations hereditary and nonhereditary | | | |
| Dominant | Recessive | | | |
| Tissue specificity may be broad | Considerable tissue specificity | | | |
| Especially leukemias and lymphomas | Solid tumors (e.g., Wilm's, retinoblastoma) | | | |

Source: From Ref. 20.

promote the effects of radiation or chemical initiators, causing concomitant stimulation of: (i) macromolecular synthesis; (ii) hyperplasia; (iii) polyamine synthesis; (iv) prostaglandin synthesis; (v) protease production; (vi) alterations of certain cell membrane enzymes and glycoproteins; (vii) induction of sister-chromatid exchanges; (viii) altered differentiation; and (ix) modified responses to various growth-controlling factors (23). Whether any one of these changes is critical for tumor promotion, however, is not clear. Traditionally, TPA and other tumor-promoting agents have been considered to act predominantly through epigenetic mechanisms (24,25), but recent observations indicate that some of these agents can damage DNA indirectly (26–29) implying that such genotoxic effects also may be involved in promotion.

Tumor progression, the process through which successive generations of neoplastic cells give rise to increasingly autonomous clonal derivatives (30), has been attributed at least in part to mutations and chromosome aberrations (15). The process can be accelerated, however, by selection pressures that favor the outgrowth of proliferative subpopulations, including repeated exposure to growth-stimulating agents and carcinogens (15,30).

EMPIRICAL DOSE-INCIDENCE RELATIONSHIPS FOR CARCINOGENSIS

Although hundreds of chemicals have been found to be oncogenic in laboratory animals, less than three dozen have been observed to be capable of inducing cancer in humans (31). With few exceptions, moreover, the relevant data are not sufficient to characterize the dose-incidence relationship except in a semiquantitative way (8).

With ionizing radiation, for which the dosimetry is less complicated by pharmacokinetic variables than is the dosimetry for most chemicals, dose-incidence data are available over a relatively wide range of radiation doses (32,33). At best, however, the data do not suffice to define the dose-incidence relationship in the low-dose domain. Assessment of the carcinogenic risks associated with low-level irradiation must thus depend on extrapolation from observations at higher levels of exposure, based on assumptions about the relevant dose-incidence relationships and mechanisms of carcinogenesis.

The extrapolation models that are used for estimating the carcinogenic risks of low-level irradiation generally assume a linear nonthreshold relationship between risk and dose in the low-dose domain, although the data do not exclude a threshold (8,33,34). Among the lines of epidemiological evidence that are consistent with a

nonthrehsold relationship are: (i) a 25-50% excess of leukemia in children exposed to diagnostic x-rays in utero. in whom the radiation dose is estimated to have averaged less than 50 mGy (35,36); (ii) an excess of thyroid tumors in persons who received therapeutic irradiation of the scalp in childhood for tinea capitis, in whom the dose to the thyroid gland is estimated to have averaged no more than 60-80 mGy (37,38); (iii) a dose-dependent excess of breast cancer, of essentially the same magnitude for a given dose, in: (a) women exposed to A bomb radiation, (b) women given the rapeutic irradiation of the breast for postpartum mastitis, (c) women who received multiple fluoroscopic examinations of the chest during the treatment of pulmonary tuberculosis with artificial pneumothorax, and (d) women exposed to external gamma radiation in the painting of luminous clock and instrument dials (33,39); and (iv) a dose-dependent excess of leukemia in A bomb survivors, which is evident at doses below 300 mGy (33,34). In each of the above populations, the doseincidence data in low-to-intermediate dose range are compatible with a linear nonthreshold relationship for the neoplasms in question. Comparable data, moreover, are available for certain radiation-induced neoplasms in laboratory animals (8,32,40,41). As concerns the carcinogenic effects of chemicals, quantitative dose-incidence data for humans are extremely limited, with few exceptions. A noteworthy exception is cigarette smoke. the major cause of lung cancer. In cigarette smokers, the incidence of lung cancer increases as a function of the number of cigarettes smoked per day raised approximately to a power of 1.8 (42). Furthermore, the absence of any clear indication of a threshold in the dose-incidence curve

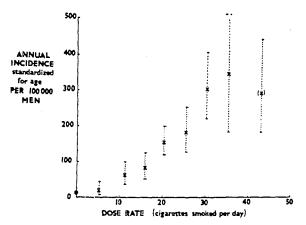


Figure 1. Annual incidence of lung cancer in regular cigarette smokers, in relation to the number of cigarettes smoked per day. (From Ref. 61.)

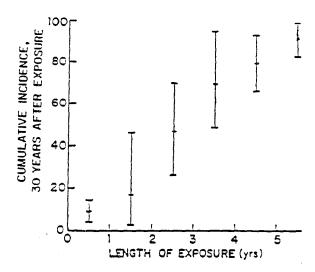


Figure 2. Cumulative incidence of cancer of the urinary bladder in 78 distillers of β -naphthylamine and benzidine. (From Ref. 8, based on data from Ref. 62.)

(Fig. 1) is consistent with epidemiological data implying that the risk of lung cancer can be increased even in nonsmokers by passive exposure to cigarette smoke over prolonged periods (43).

Other populations for which the dose-incidence data are compatible with a nonthreshold type of response include groups of chemists who were employed as distillers of 2-naphthylamine. In one such group, the cumulative incidence of cancer of the urinary bladder was observed to increase with the duration of occupational exposure, approaching 100% in workers who were exposed for five years or longer (Fig. 2).

In asbestos workers, likewise, the rates of lung cancer and mesothelioma appear to increase linearly with the intensity and duration of exposure (44). Furthermore, in asbestos workers who smoke cigarettes, the combined carcinogenic effects of asbestos and cigarette smoke appear to be multiplicative rather than merely additive (Table 2), implying that the two agents exert their effects through complementary rather than similar mechanisms.

With respect to the mechanism of cigarette smokeinduced carcinogenesis, it is noteworthy that the excess of lung cancer in ex-smokers stops rising relatively promptly after cessation of smoking (45), suggesting that cigarette smoke affects primarily late stages of carcinogenesis. The carcinogenic effects of cigarettes thus stand in contrast to those of radiation (33) and asbestos (46), which continue to become manifest for decades after exposure. 270 Upton

Table 2

Age-Standardized Lung Cancer Death Rates as Affected by Cigarette Smoking, Occupational Exposure to Asbestos Dust, or Both^a

| Exposure to asbestos | History of cigarette smoking | Death rate | Mortality difference | Mortality ratio |
|----------------------|------------------------------|------------|----------------------|-----------------|
| No | No | 11.3 | 0.0 | 1.00 |
| Yes | No | 58.4 | +47.1 | 5.17 |
| No | Yes | 122.6 | +111.3 | 10.85 |
| Yes | Yes | 601.6 | +590.3 | 53.24 |

^aAge-standardized lung cancer death rates are rates per 100.000 man-years standardized for age on the distribution of the man-years of all the asbestos workers. Number of lung cancer deaths based on death certificate information.

Source: From Ref. 59.

Because of the multicausal, multistage nature of carcinogenesis and the fact that the mechanism of carcinogenesis is not the same for all cancers and all agents, some diversity of dose-incidence relationships is to be expected. The neoplasms that are induced by a given chemical in different tissues or in animals of different species also may vary in dose-incidence relationships because of pharmacogenetic and pharmacokinetic differences affecting the dosage of carcinogen to different target cells (47). The observed age- and tissue-dependent variations in dose-incidence relationhips among radiation-induced neoplasms are largely unexplained as yet (41), but differences in cell proliferation kinetics and homeostatic ability (including capacity to repair DNA damage) may constitute potential sources of such variation (20).

To explore the dose-incidence curve for carcinogenesis at low doses, a number of large-scale experiments have been carried out with laboratory animals. In the largest of these to date, the incidence of hepatomas in mice was observed to increase with the concentration of 2-AAF in the diet even at the lowest dose level tested (Fig. 3), whereas the dose-incidence curve for tumors of the urinary bladder was quasithresholded (Fig. 3). This contrast in dose-incidence curves may have resulted from differences between the liver and the bladder in the metabolism of 2-AAF among other explanations.

Because a given carcinogen may influence the probability of neoplasia through more than one type of effect, at least at high dose levels, its dose-incidence curve can reflect differing combinations of initiating effects, promoting effects, and anticarcinogenic effects, depending on the dose and other circumstances. The combined effects of multiple agents may, likewise, be additive, synergistic, or antagonistic, depending on the agents in question and the conditions of exposure. At low to moderate dose levels, the effects of a complete carcinogen can generally be accentuated by appropriate tumor-promoting stimuli,

which unmask initiating effects that would otherwise remain unexpressed (Fig. 4). It is noteworthy, moreover, that under conditions in which initiating effects are promoted to full expression they often increase as a linear nonthreshold function of the dose of the initiating agent (Fig. 4). Furthermore, whereas the carcinogenic effectiveness per unit dose of x-rays and gamma rays tends to

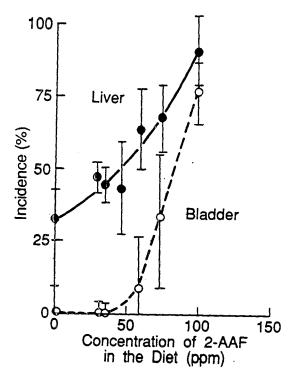
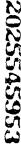


Figure 3. Cumulative incidence of tumors of the liver and of the urinary bladder in female BALB/c mice exposed to 2-acetylaminofluorene (2-AAF) at various concentrations in the diet for up to 33 months. (From Ref. 63.).



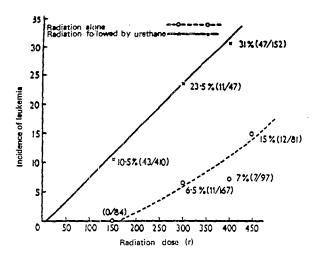


Figure 4a. Cumulative incidence (in percent) of leukemia in C57BL mice in relation to the dose of whole-body x-radiation administered in a single exposure (--o-o-), with or without subsequent injections of urethane (-x-x-). (Reproduced from Ref. 64.)

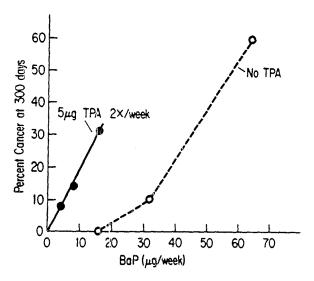


Figure 4b. Cumulative incidence of carcinomas of the skin in mice exposed once weekly to benzo(a)pyrene (BaP), with or without subsequent exposure to 12-O-tetradecanoyl phorbol-13-acetate (TPA) twice weekly. Doses refer to the amount of B(a)P applied to the skin each week. (Reproduced from Ref. 65.)

decrease with decreasing dose and dose rate, that of high-LET radiation tends to remain constant or even increase (Fig. 5) (32,40,41).

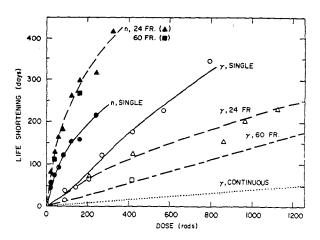


Figure 5. Life shortening (all causes) in male B6CF, mice in relation to the total dose of single, fractionated (FR), or continuous whole-body neutron- or gamma-irradiation. (Reproduced from Ref. 66.)

Cell Transformation In Vitro

The neoplastic transformation of cells in vitro, although not strictly analogous to carcinogenesis in vivo, provides a model system that can be helpful in identifying carcinogenic agents and exploring their mechanisms of action. Few detailed dose-response curves for cell transformation have been published as yet, but the morphological transformaton of Syrian hamster embryo cells by benzo(a)pyrene (BAP) (48,49) is consistent with one-hit kinetics except at cytotoxic dose levels (50). A one-hit model also holds for the transformation of such cells by the combined effects of x-rays and BAP (50). With x-rays alone, the frequency of transformation per surviving cell is increased by a dose as low as 10 mGy, above which it appears to increase curvilinearly with the dose up to 1.5 Gy; however, a linear increase over the same dose range cannot be excluded (51). Although the rate of transformation per unit dose typically decreases on protraction or fractionation of exposure to gamma rays, it may increase on protraction or fractionation of exposure to fast neutrons (Fig. 6).

In C3H101/2 cells irradiated in vitro—as well as in thyroid and mammary "clonogens" irradiated in vivo (52)—"initiation" appears to occur with a frequency as high as 0.01–0.1 per cell per Gy (53) and to increase as a linear nonthreshold function of the dose (Fig. 7). The subsequent, final transforming event in such cells is far rarer, however, occurring at a rate of only 10^{-6} to 10^{-7} per cell generation (53,54).

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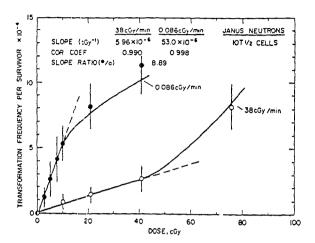


Figure 6. Frequency of neoplastic transformation in C3H 10T1/2 cells exposed to fission-spectrum neutrons. Dashed lines indicate linear regressions fitted to the initial portions of the dose-effect curves. (Reproduced from Ref. 67.)

Interpolation and Extrapolation Models

Although the relation between the incidence of neoplasia and the dose of carcinogen is known to vary with the type of neoplasm, the carcinogen, and other variables, the dose-incidence relationships at low doses is not known precisely for any neoplasm or carcinogen. The risks of low-level exposure to a cancer-causing agent can thus be assessed only through interpolation or extrapolation from effects observed at higher levels of exposure. For many of the neoplasms induced by ionizing radiation, the doseincidence relation generally conforms to the patterns illustrated in Figure 8, which are consistent with those to be expected if the probability of carcinogenesis could be increased in a suitably susceptible individual by an appropriate mutation or chromosomal aberration in a single somatic cell. Under this assumption, the dose-incidence curve for high-LET radiation would be expected to conform, in general, to the expression:

$$I = C + aD \tag{1}$$

where I is the incidence at dose D, C is the incidence in nonirradiated controls, and the coefficient a is a constant; similarly, for low-LET radiation, the dose-incidence curve would conform, in general, to the expression:

$$I = (C + aD + bD^{2})e^{-(pD+qD^{2})}$$
 (2)

where the symobls are comparable to those above, except for a different value of the coefficient a and the addition of the coefficients b, p, and q (55).

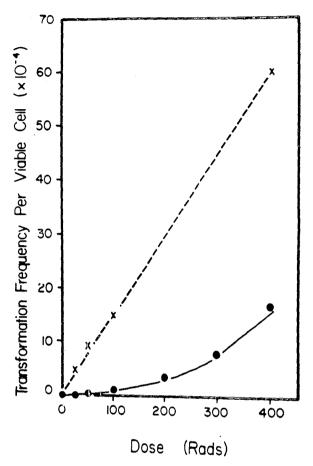


Figure 7. Dose-response relationship for the induction of neoplastic transformation in mouse 10T1/2 cells by x-rays alone (0), or by x-rays followed by phorbol ester, starting 48 h after irradiation and continued for the full 6-week expression period (•). No increase in transformation frequency was detected following exposure to phorbol ester alone. (Reproduced from Ref. 68.)

While many of the observed dose-incidence curves conform to the latter pattern, the curve for radiation-induced breast cancer appears more nearly linear, as noted above. To allow for uncertainty about the shape of the dose-incidence curve at low doses and thus to obtain a range of reasonable risk estimates, alternative models (Figs. 9 and 10) have been used in assessing the risks of low-level exposure to carcinogens. Most such models treat carcinogenesis as a multicausal, multistage process. Depending on the particular model that is used for interpolation or extrapolation, however, the estimated risk at low doses can vary by order of magnitude (e.g., Table 3). The linear (one-hit) model for interpolating between the lowest dose

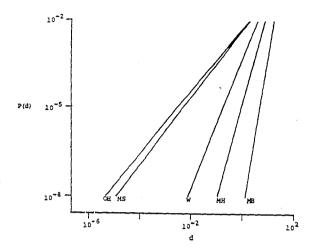


Figure 8. Estimated risk of liver cancer, p(d), in relation to the dose of aflatoxin, d, as determined with different dose-incidence models; i.e., OH, one-hit model; MS, multistage model; W, Weibull model; MH multihit model; and MB, Mantel-Bryan (log-probit model). (From Ref. 56.)

Table 3

Estimated Risk of Cancer of the Human Urinary Bladder from Daily Ingestion of 0.12 g of Saccharin

| Method of transspecies scaling and of high- to low-dose extrapolation | Lifetime cases per million exposed |
|---|--|
| Rat dose adjusted to human dose by surface area rule | |
| Single-hit model | 1,200 |
| Multistage model (with quadratic term) | 5 |
| Multihit model | 0.001 |
| Mantel-Bryan probit model | 450 |
| Rat dose adjusted to human dose by mg/kg/day equivalence | |
| Single-hit mode! | 210 |
| Multihit model | 0.001 |
| Mantel-Bryan probit model | 21 |
| Rat dose adjusted to human dose by mg/kg/lifetime equivalence | |
| Single-hit model | 5,200 |
| Multihit model | 0.001 |
| Mantel-Bryan probit model . | 4,200 |

Source: From Ref. 60.

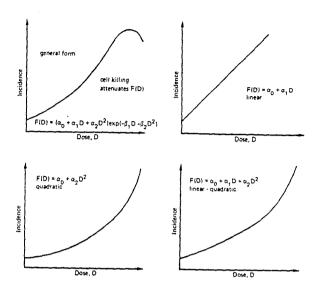


Figure 9. Dose-response curves for four different mathematical models relating cancer incidence to radiation dose which were evaluated by the National Academy of Sciences Advisory Committee on the Biological Effects of Ionizing Radiation. (From Ref. 33.)

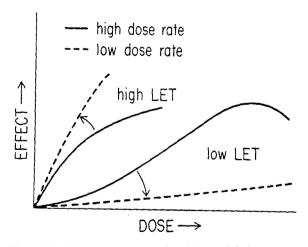


Figure 10. Diagrammatic representation of characteristic dose-response curves, relating the incidence of tumors in laboratory animals to the dose and dose rate of high-LET (——) radiation and low-LET (——) radiation. (Reproduced from Ref. 69.)

at which a significantly increased incidence has been observed and the baseline (zero dose) incidence is generally thought to overestimate the risk at low doses (8,56), and thus to provide an "upper limit" estimate of risk, with the lower limit of the range extending to zero.

Although the mechanisms of action of carcinogens of different types are still to be defined precisely, the existing data suggest that a linear nonthreshold interpolation model may be appropriate only for an initiating agent or a complete carcinogen, and that a model yielding a smaller estimate of the risk at low doses is more likely to be appropriate for a promoting agent. Similarly, for a chemical that is activated through nonlinear metabolic processes (57) or that acts through toxic effects elicited only at relatively high doses (e.g., immunosuppression) (58), a threshold or quasithreshold dose-incidence model is likely to be more appropriate.

In view, however, of the existence within the human population of individuals who vary widely in their susceptibility to cancer, as well as those who are at different stages of carcingenesis as a result of the action of other cancer-causing agents or risk factors, it is assumed that a carcinogen may pose some degree of risk to the population at any dose, by exerting carcinogenic effects that are additive with those which account for the "spontaneous" baseline incidence of cancer (Fig. 11). Hence, unless an agent can be shown to act through effects that are not additive with those which account for the "spontaneous" baseline incidence of cancer, a nonthreshold model is generally recommended for assessing the carcinogenic risks of the agent for public health purposes.

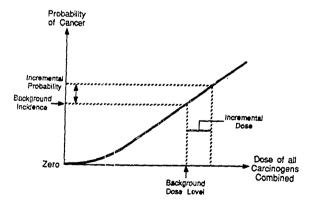


Figure 11. Diagram illustrating the expected increment in risk of cancer resulting from a low dose of a hypothetical carcinogen. Because cellular effects similar to those of the carcinogen may be produced in its absence by "background" mechanisms, the effects resulting from low doses of that carcinogen may be additive with those resulting from other "background" risk factors, thus causing an increase in the risk that is proportional to the dose. (From Ref. 70.)

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REFERENCES

- Muller HJ: The manner of production of mutations by radiation. In Radiation Biology Vol. 1. High Energy Radiation. Edited by A Hollaender. McGraw-Hill, New York, 1954, pp 475-626.
- United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR). Report of the Scientific Committee on the Effects of Atomic Radiation. United Nations, New York, 1958.
- United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR). Genetic and Somatic Effect of Ionizing Radiation. Report to the General Assembly, with Annexes. United Nations, New York, 1986.
- 4. Auerbach C: Chemical mutagenesis. Biol Rev 24:355-391, 1949.
- Ehling UH, Averbeck D, Cerutti PA, et al: Review of the evidence for the presence or absence of thresholds in the induction of genetic effects of genotoxic chemicals. International Commission for Protection Against Environmental Mutagens and Carcinogens. ICPEMC Publication No. 10. Mutat Res 123:281-341, 1983.
- Lewis EB: Leukemia and ionizing radiation. Science 125:965-975. 1957.
- Scherer E, Emmelot P: Multihit kinetics of tumor cell formation and risk assessment of low doses of carcinogen. In Carcinogens: Identification and Mechanisms of Action. Edited by AC Griffin, CR Shaw. Raven Press, New York, 1979, pp 337-364.
- Zeise L, Wilson R, Crouch EAC: The dose response relationships for carcinogens: a review. Env Health Perspect 1988 73:259–306, 1987.
- Fialkow PJ: Clonal origin of human tumors. Biochim Biophys Acta 458:283-321, 1979.
- Ponder BAJ: Genetics and cancer. Biochim Biophys Acta 605: 368-410, 1980.
- Sandberg AA: A chromosomal hypothesis of oncogenesis. Cancer Genet Cytogenet 8:277-285, 1983.
- Farber E, Sarma DSR: Biology of disease. Hepatocarcinogenesis:
 A dynamic cellular perspective. Lab Invest 56:4-22, 1987.
- Nicholson GL: Tumor cell instability, diversification, and progression to the metastatic phenotype: from oncogene to oncofetal expression. Cancer Res 47:1473-1487, 1987.
- Barrett JC, Crawford BD, Ts'o POP: The role of somatic mutation in a multistage model of carcinogenesis. In Mammalian Cell Transformation by Chemical Carcinogens. Edited by N Mishra, VC Dunkel, M Mehlman, Senate Press, Princeton Junction, NJ, 1980, p 467.
- Farber E: Cellular biochemistry of the stepwise development of cancer with chemicals: G.H.A. Clowes Memorial Lecture. Cancer Res 44:5463-5474, 1984.
- Barrett JC, Elmore E: Comparison of carcinogenesis and mutagenesis of mammalian cells in culture. In Handbook of Experimental

- Pharamcology. Edited by LS Andrews, RJ Lorentzen, WD Flamm. Springer-Verlag, Berlin, 1984, pp 171-206.
- Bertram JS, Heidelberger C: Cell cyclic dependency of oncogenic transformation induced by N-methyl-N'-nitro-N-nitrosoguanidine in culture. Cancer Res 34:526-537, 1974.
- Bates RR, Eaton SA, Morgan DL, et al: Replication of DNA after binding of the carcinogen 7-dimethylbenz[a]anthracene. J Natl Cancer Inst 45:1223-1228, 1970.
- Kakunaga T: Requirement for cell replication in the fixation and expression of the transformed state in mouse cells treated with 4-nitroquinoline-1-oxide. Int J Cancer 14:736-742, 1974.
- Knudson AG: Hereditary cancer, oncogenes, and antioncogenes. Cancer Res 45:1437, 1985.
- Huberman E, Mager R, Sachs L: Mutagenesis and transformation of normal cells by chemical carcinogenesis Nature 204:360-361, 1976.
- Parodi S, Brambilla G: Relationship between mutation and transformation frequencies in mammalian ceils treated in vitro with chemical carcinogens. Mutat Res 47:53-74, 1977.
- Blumberg PM: In vitro studies on the mode of action of the phorbol esters, potent tumor promoters, Part 1 and 2. CRC Crit Rev Toxicol 3:152-234, 1980, 1981.
- Weinstein IB, Gatto-Celli S, Kirschmeier P, et al: Cellular targets and host genes in multistage carcinogenesis. Fed Proc 43:2287-2294, 1984.
- 25. Weinstein IB: Cell culture studies on the mechanism of action of chemical carcinogens and tumor promoters. In Carcinogenesis, a Comprehensive Survey. Vol. 10. The Role of Chemicals and Radiation in the Etiology of Cancer. Edited by E Huberman, SH Barr. Raven Fress, New York, 1985, pp 177-187.
- Cerutti PA, Amstad P, Emerit I: Tumor promoter phorbolmyristate-acetute induced membrane-mediated chromosoma damage. In Radioprotectors and Anticarcinogens. Edited by OF Nygaard. MG Simic. Academic Press, New York, 1983, pp 527-538.
- Upton AC, Clayson DG, Jansen D, et al: Report of ICPEMC task group on the differentiation between genotoxic and non-genotoxic carcinogens. Mutat Res 133:1-49, 1984.
- Troll W, Weisner R: The role of oxygen radicals as a possible mechanism of tumor promotion. Ann Rev Pharmacol Toxicol 25:509-528, 1985.
- Liehr JG, Randerath K, Randerath E: Target organ-specific covalent DNA damage preceding diethylstilbestrol-induced carcinogenesis. Carcinogenesis 6:1067-1069, 1985.
- Foulds L: Neoplastic Development, Vol. 1. Academic Press, New York, 1969.
- 31. International Agency for Research on Cancer (IARC): On the Evaluation of the Carcinogenic Risk of Chemicals to Humans, Chemicals, Industrial Processes, and Industries Associated with Cancer in Humans, Supplement 4. IARC Monograph, Lyon, International Agency for Research on Cancer, 1982.
- United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR): Sources and Effects of Ionizing Radiation. Report to the General Assembly, with Annexes. United Nations, New York, 1977.
- National Academy of Sciences, Advisory Committee on the Biological Effects of Ionizing Radiation. (NAS/BEIR): The Effects on Populations of Exposure to Low Levels of Ionizing Radiation. National Academy of Science, Washington, DC, 1980.
- Rall JE, Beebe GW, Hoel DG, et al: Report of the National Institutes of Health Working Group to Develop Radioepidemiological

- Tables, NIH Publication No. 85-2748. U.S. Government Printing Office, Washington, DC, 1985.
- Monson RP, MacMahon B: Pre-natal x-ray exposure and cancer in children. In Radiation Carcinogenesis: Epidemiology and Biological Significance. Edited by JD Boice Jr, JF Fraumeni Jr. Raven Press, New York, 1984, pp 97-105.
- Harvey EB, Boice JD Jr, Honeyman M, et al: Prenatal x-ray exposure and childhood cancer in twins. N Engl J Med 12:541-545, 1985
- Modan B, Ron E, Werner A: Thyroid cancer following scalp irradiation. Radiology 123:741-744, 1977.
- Shore RE, Woodard ED, Hemplemann LH, et al: Syngerism between radiation and other risk factors for breast cancer. Prev Med 9:815-822, 1980.
- Boice JD Jr, Land CE, Shore RE, et al: Risk of breast cancer following low-dose exposure. Radiology 131:589-597, 1979.
- Broerse JJ, Gerber GB (Eds): Neutron Carcinogenesis. Luxembourg, Commission of the European Communities, Luxembourg. 1982.
- Upton AC: Biological basis for assessing carcinogenic risks of low-level radiation. In Carcinogenesis, a Comprehensive Survey. Vol. 10. The Role of Chemicals and Radiation in the Etiology of Cancer. Edited by E Huberman, SH Barr. Raven Press, New York, 1985, pp 381-401.
- Doll R, Peto R: The cause of cancer: quantitative estimates of avoidable risk of cancer in the United States today. J Natl Cancer Inst 66:1192-1308, 1981.
- National Research Council (NRC), Committee on Passive Smoking: Environmental Tobacco Smoke: Measuring Exposures and Assessing Health Effects, National Academy Press, Washington, DC, 1986.
- Nicholson GL: Airbon Assessment Update, publication No. EPA-600-8-84-003F. U.S. Environmental Protection Agency, Washington, DC, 1985.
- Doll R: Cancer and aging: The epidemiologic evidence. Oncology 5:1-28, 1970.
- Hammond EC, Selikoff IJ, Seidman H: Asbestos exposure, cigarette smoking and death rates. Ann NY Acad Sci 330:473-490, 1979.
- Wilkinson GR: Pharmacokinetic considerations in toxicology. In Drug Metabolism and Drug Toxicology. Edited by JR Mitchell, MG Horning. Raven Press, New York, 1984, pp 213-235.
- Huberman E, Sachs L: Cell susceptibility to transformation and cytotoxicity by the carcinogenic hydrocarbon benzo[a]pyrene. Proc. Natl Acad Sci (USA) 56:1123-1129, 1966.
- DiPaolo JA, Donovan PJ, Nelson RL: In vitro transformation of hamster cells by polycyclic hydrocarbons: factors influencing the number of cells transformed. Natures New Biol 230:240-242, 1971.
- Gart JJ, DiPaolo A, Donovan PJ: Mathematical models and the statistical analyses of cell transformation experiments. Cancer Res 39:6069-6075, 1979.
- Borek C, Hall EJ: Transformation of mammalian cells in vitro by low doses of x-rays. Nature 243:450-453, 1973.
- Clifton KA, Kamiya K, Milcahy RT, et al: Radiogenic neoplasia in the thyroid and mammary clonogens: progress, problems, and possibilities. In Assessment of Risk from Low-Level Exposure to Radiation and Chemicals, A Critical Overview. Edited by AD Woodhead, CJ Shellabarger, V Bond, A Hollaender. Plenum Press, New York, 1985, pp 329-344.
- 53. Kennedy AR, Little JB: Evidence that a second event in

i

- x-ray-induced oncogenic transformation in vitro occurs during cellular proliferations. Radiat Res 99:228-248, 1984.
- Kennedy A: The condition for the modification of radiation transformation in vitro by a tumor promoter and protease inhibitors. Carcinogenesis 6:1441-1445, 1985.
- Upton AC: Radiobiological effects of low doses; implications for radiological protection. Radiat Res 71:51-74, 1977.
- Krewski D, Van Ryzin J: Dose response models for quantal response toxicity data. In Statisticul and Related Topics. Edited by J Sxorgo. D Dawson, JNK Rao, E. Shaleh, North Holland. New York, 1981, pp 201-231.
- Hoel DG, Kaplan NL, Anderson MW: Implication of nonlinear kinetics on risk estimation in carcinogenesis. Science 219: 1023-1037, 1983.
- Old LJ: Cancer immunology: the search for specificity. G. H. A. Clowes Memorial Lecture. Cancer Res 41:361, 1981.
- Selikoff JJ: Constraints in estimating occupational contributions to current cancer mortality in the United States. In Quantification of Occupational Cancer. Banbury Report 9. Edited by R Peto. M Schneiderman, Cold Spring Harbor Laboratory, Cold Spring Harbor, 1981, pp 3-13.
- 60. National Academy of Sciences (NAS): Saccharin: Technical Assessments of Risks and Benefits. Part 1 of a 2-Part Study of the Committee for a Study of Saccharin and Food Safety Policy. Panel 1: Saccharin and Its Impurities. Assembly of Life Sciences/National Research Council and the Institute of Medicine. National Academy of Sciences, Washington, DC, 1978.
- Doll R: An epidemiological perspective of the biology of cancer. Cancer Res 38:3573-3583, 1978.

- Williams MHC: Occupational tumors of the bladder. In Cancer. Edited by RW Raven. Butterworth. London, 1958, p 337.
- Littlefield NA, Farmer JH, Gaylor DW: Effects of dose and time in a long-term, low-dose carcinogenic study. J Environ Pathol Toxicol 3:17-34, 1979.
- Berenblum I, Trainin, N: New evidence of the mechanism of radiation leukacmogenesis. In Cellular Basis and Aetiology of Late Somatic Effects of Ionizing Radiation. Edited by RJC Harris. Academic Press, New York, 1963, pp 41-56.
- Burns FJ, Albert RE: Mouse skin papillomas as early stage of carcinogenesis. J Am Coll Toxicol 1:29-45, 1982.
- 66. Thomson JF, Lombard LS, Grahn D, et al: RBE of fission neutrons for life shortening and tumorigenesis. In Neutron Carcinogenesis. Edited by J Broerse, GB Gerber, Luxembourg, Commission of the European Communities, 1982, pp 75-94.
- Hill CK, Han A, Elkind MM: Fission-spectrum neutrons at low dose rate enhance neoplastic transformation in the linear, low dose region (0-10 Gy). Int J Radiat Biol 46:11, 1984.
- Little JB: Influence of noncarcinogenic secondary factors on radiation carcinogenesis. Radiat Res 87:240-250, 1981.
- Upton AC: Biological aspects of radiation carcinogenesis. In Radiation Carcinogenesis: Epidemiology and Biological Significance. Edited by JD Boice Jr. JF Fraumeni Jr., Raven Press, New York, 1984, pp 9-19.
- National Council on Radiation Protection (NCRP): Comparative Carcinogenicity of Ionizing Radiation and Chemicals. Washington. DC, National Council on Radiation Protection and Measurement. 1080

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Are There Thresholds for Carcinogenesis?^a

The Thorny Problem of Low-Level Exposure

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INTRODUCTION

Few issues in health policy are more contentious than the choice of the appropriate dose-incidence model for use in estimating the risks of cancer associated with low-level exposure to a carcinogen. The notion that there may be no threshold for carcinogenic effects—namely, that some degree of risk may be associated with the lowest dose of carcinogen—seems to contradict everyday experience that teaches us that essentially no other type of insult produces a lasting injury unless it exceeds some threshold of severity.

In the past, toxicological risk assessments have traditionally been based on the concept of a no-effect level. The applicability of this concept to mutagenic effects, however, came to be questioned by the middle of the century. Since then, the applicability of the concept to carcinogenic effects—which likewise may conceivably be mediated through effects on individual cells, rather than groups of cells—also has been challenged.

In principle, of course, it is not possible to prove or disprove the existence of an absolute threshold for carcinogenesis. Hence the argument for or against the threshold hypothesis must be based on theoretical as well as empirical evidence.² Some of the salient lines of evidence are summarized briefly in the following.

BIOLOGY OF CARCINOGENESIS

Unicellular, Monoclonal Origin of Cancer

The monoclonal origin of cancer is suggested by enzymological studies of human tumor cells, in which X-linked glucose-6-phosphate dehydrogenase has been used as a marker.³ Similar evidence has come from studies of chemically induced tumors of chimeric mice, in which glucose phosphate isomerase has been used as a marker.^{4,5} Cytogenetic analysis of tumor cells has also suggested their monoclonal nature.⁶

The evidence that cancer usually originates from a single precursor cell implies, as does the heritable nature of the malignant phenotype, that appropriate damage to one cell alone may suffice to increase the probability of the disease in a

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suitably susceptible individual. The data also indicate, however, that more than one alteration is necessary to convert a normal cell into a cancer cell, as discussed below.

Multicausal, Multistage Nature of Carcinogenesis

Clinical, pathological, and experimental data imply that cancer evolves through at least three successive stages: initiation, promotion, and progression.⁷

Initiation

Initiation, which starts the process, does not itself suffice to cause neoplasia but predisposes the affected cell and its progeny to subsequent steps in carcinogenesis. The initiated cell may not be recognizable as such, however, or may never form a tumor, unless it is further altered by subsequent tumor-promoting stimulation. The mechanism of tumor initiation remains to be established, but some type of mutational process is suggested by the evidence that 1) initiation is relatively prompt and irreversible; 2) most ultimate carcinogens are mutagens; 3) the frequency of cell transformation induced by a given carcinogen usually is highest if exposure to the agent occurs just before or during the DNA synthetic phase of the cell cycle⁸; 4) DNA to which a chemical carcinogen is bound can serve as a template for DNA replication⁹; 5) after exposure to a carcinogen, DNA synthesis and subsequent cell division "fix" the potential for neoplastic change 10; 6) in a given biological system, the carcinogenic potency of an initiating chemical is generally correlated with the extent to which it binds covalently to DNA, and with the nature of the resulting reaction products; and 7) susceptibility to cancer is increased in persons who are deficient in DNA repair. 11 The frequency of neoplastic transformation is far higher, however, than that of single gene mutation in cells exposed to genotoxic carcinogens^{12,13}; hence, the data implicate multiple oncogenic sites, damage of the genome at sites unlikely to be repaired (for example, tandem repeats), or genetic damage other than point mutations. 14 The specific genes that may be involved are only beginning to be defined but appear to include antioncogenes as well as oncogenes. 11 It is noteworthy, furthermore, that activation and expression of more than one oncogene appears to be necessary for cell transformation in vitro. 15

Tumor Promotion

Tumor promotion is the process that results in the additional change, or changes, necessary to cause the neoplastic transformation of an initiated cell. In contrast to initiation, which can result from a single exposure to an appropriate tumor-initiating agent, tumor promotion requires repeated and sustained stimuli. Although tumor promotion has been demonstrated in a number of tissues, its mechanisms have thus far been studied systematically only in a few model systems. In one of these, the mouse skin model, nanomolar concentrations of the tumor-promoting phorbol ester 12-0-tetradecanoylphorbol-13-acetate induce stimulation of 1) macromolecular synthesis; 2) hyperplasia; 3) polyamine synthesis; 4) prostaglandin synthesis; 5) protease production; 6) alterations of cell membrane enzymes and glycoproteins; 7) induction of sister-chromatid exchanges; 8) altered

differentiation; and 9) modified responses to other growth-controlling factors. ¹⁶ Such effects have also been demonstrated, *in vivo* and *in vitro*, in cells of various other species, including man. As yet, however, it is not known whether any of these responses is critical for tumor promotion. Furthermore, although all tumor-promoting agents induce cellular proliferation in their respective target tissues, each appears to be relatively tissue-specific. The capacity of the promoters to induce pleiotropic effects at nanomolar concentrations and their discrete structure-activity relationships implicate a hormone-like mode of action. ¹⁷⁻¹⁹

Agents that possess initiating activity as well as promoting activity can cause neoplasia by themselves if given in sufficient doses. The effects of such "complete" carcinogens can be enhanced, however, by various other agents that are not active by themselves but can potentiate the effects of carcinogens if given simultaneously with them.²⁰ Such "co-carcinogens," which include certain phenols, aliphatic hydrocarbons, and aromatic hydrocarbons, are prevalent in the environment and appear to act by altering the uptake, distribution, and/or metabolism of carcinogens, or by enhancing the susceptibility of the target cells or host.²⁰ Tumor promoters have thus traditionally been considered to act predominantly through epigenetic mechanisms.¹⁸ Recently, however, the production of indirect damage to DNA, resulting in mutations and chromosome aberrations, has been implicated in a growing number of instances²¹⁻²³; for example, target organ-specific DNA adducts have been identified in association with the carcinogenic effects of diethylstilbesterol on the hamster kidney.²⁴

Tumor Progression

Tumor progression is a process through which successive alterations in neoplastic cells give rise to increasingly autonomous clonal derivatives.²⁵ The precise nature of such alterations remains to be determined, but mutations and chromosome aberrations have been tentatively implicated.⁷ Tumor progression may be accelerated by repeated exposure of neoplastic cells to carcinogenic stimuli or by selection pressures that favor the outgrowth of increasingly autonomous subpopulations of cells.

EPIDEMIOLOGIC DATA ON DOSE-INCIDENCE RELATIONSHIPS IN HUMANS

In contrast to the hundreds of chemicals that have been observed to possess oncogenic activity in laboratory animals, less than three dozen are known to induce cancer in man.²⁶ In few cases, moreover, are the relevant epidemiological data adequate to characterize the relationship between cancer incidence and the dose of a given carcinogen, except in a semiquantitative way.

Analysis of the dose-incidence relationship is less difficult with ionizing radiation than with carcinogenic chemicals because dosimetry with radiation is not complicated in the same way by pharmacokinetic variables. Furthermore, incidence data for irradiated populations are available over a wide range of radiation doses, ^{27,28} whereas comparable dose-incidence data for chemicals are generally lacking. In no case, however, do the data suffice to define the dose-incidence relationship in the low dose domain or to exclude the possibility of a threshold. Hence assessment of the carcinogenic risk associated with low-level exposure to

any carcinogenic agent must depend on extrapolation from observations at higher dose levels, based on assumptions about the relevant dose-incidence relationships and mechanisms of carcinogenesis.

The extrapolation models generally used for estimating the carcinogenic risks of low-level irradiation are of the nonthreshold type; that is, the linear non-threshold model or the "linear-quadratic" nonthreshold model is usually used. ^{28,29} The strongest epidemiological evidence in support of these models consists of (1) the large excess of acute leukemia and other juvenile malignancies that is associated with a dose as low as 1-5 rad in utero^{30,31}; (2) the excess of thyroid

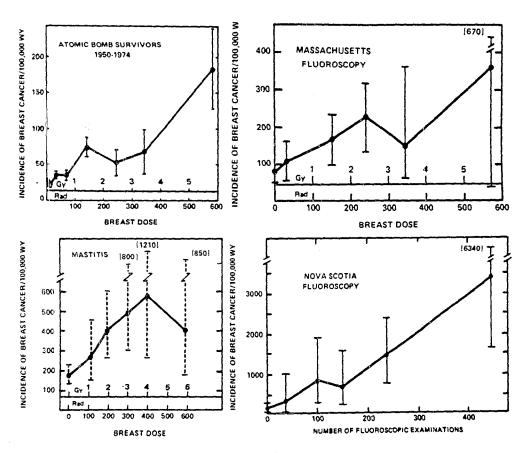


FIGURE 1. Incidence of cancer of the female breast as a function of dose in A-bomb survivors, in women treated with X-rays for acute postpartum mastitis, and in women subjected to multiple fluoroscopic examinations of the chest during treatment of pulmonary tuberculosis with artificial pneumothorax. (Reproduced from Boice et al.³⁴ with permission from the Radiological Society of North America.)

tumors that occurs following epilating irradiation of the scalp for tinea capitis in childhood, which is associated with an average dose to the thyroid gland of only 6-8 rad; 32,33 (3) the excess of breast cancers (Fig. 1) in (a) women exposed to Abomb radiation, (b) women given therapeutic irradiation for postpartum mastitis, (c) women who received multiple fluoroscopic examinations of the chest during the treatment of pulmonary tuberculosis with artificial pneumothorax, and (d) women exposed occupationally to external gamma radiation in the painting of

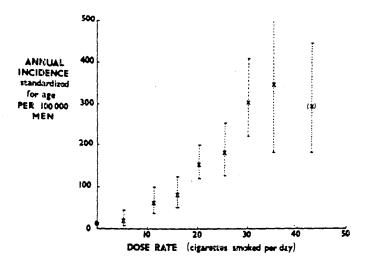


FIGURE 2. Incidence of lung cancer in regular smokers of cigarettes in relation to the number of cigarettes smoked per day. (Reproduced from Doll³⁵ with permission.)

luminous clock and instrument dials, which is similar in all four groups, irrespective of the marked differences among the groups in the duration of exposure^{28,34}; and (4) the excess of leukemia in A-bomb survivors, which is evident at doses below 0.25 Gy.^{28,29} The data from each of these studies, although not adequate to precisely define the shape of the dose-incidence curve in the low dose domain, are compatible with linear nonthreshold functions for each of the neoplasms in question.



With respect to the carcinogenic effects of chemicals, as opposed to ionizing radiation, quantitative dose-incidence information for human populations is far more limited. Nevertheless, considerable information is available for a few chemicals, one of them being cigarette smoke, which contains thousands of compounds, including initiating agents as well as promoting agents. In cigarette smokers, the incidence of lung cancer (Fig. 2) increases as a function of the average number of cigarettes smoked per day raised to a power of 1.8.³⁶

Similarly, in chemists who were employed as distillers of 2-napthylamine, the cumulative incidence of cancer of the urinary bladder increases steeply with the duration of occupational exposure, approaching 100% in those who were exposed for 5 years or longer (Fig. 3).

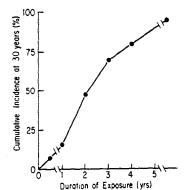


FIGURE 3. Cumulative incidence of tumors of the urinary bladder, at 30 years after start of exposure in 78 distillers of 2-naphthylamine and benzidine, in relation to duration of occupational exposure. (Reproduced from Saffiotti³⁷ [based on data from Williams³⁸] with permission from the International Agency for Research on Cancer.)

In asbestos workers, likewise, the incidence of lung cancer and of mesothelioma appears to increase linearly with the intensity and duration of exposure.³⁹ It is noteworthy, furthermore, that in cigarette smokers who have also been exposed occupationally to asbestos, the carcinogenic effects of cigarette smoke and asbestos appear to interact multiplicatively rather than additively (Table 1).

Also noteworthy is the fact that the excess of lung cancer in ex-smokers decreases rapidly after cessation of smoking,⁴¹ suggesting that cigarette smoke affects primarily on late stages of carcinogenesis, acting as a promoting agent. This situation contrasts sharply with that in irradiated²⁸ or asbestos-exposed⁴² populations, in whom the risk of lung cancer persists long after exposure.

EXPERIMENTAL DOSE-EFFECT DATA

Carcinogenesis in Laboratory Animals

The neoplasms induced experimentally in animals of different species vary widely in dose-incidence relationships. Although neoplasms of virtually every

TABLE 1. Age-Standardized Lung Cancer Death Rates for Cigarette Smoking, Occupational Exposure to Asbestos Dust, or Both

| Group | Exposure to Asbestos? | History of Cigarette Smoking? | Death Rate | Mortality Difference | Mortality Ratio |
|------------------|-----------------------------|-------------------------------|---------------|-------------------------|--------------------|
| Control | No | No | 11.3 | 0.0 | 1.00 |
| Asbestos workers | Yes | No | 58.4 | +47.1 | 5.17 |
| Control | No | Yes | 122.6 | +111.3 | 10.85 |
| Asbestos workers | Yes | Yes | 601.6 | +590.3 | 53.24 |

Note: Age-standardized lung cancer death rates are rates per 100,000 man-years standardized for age on the distribution of the man-years of all the asbestos workers. Number of lung cancer deaths based on death certificate information. (Adapted from Selikoff.⁴⁰)

type have been induced in one experiment or another, all types of neoplasms are not elicited in animals of any one species or strain. In fact, certain types of neoplasms actually decrease in frequency with increasing dose of whole-body irradiation (Fig. 4).

Among chemically induced neoplasms, the observed variations are attributable in part to pharmacokinetic differences affecting the dosage of carcinogen to different cells and subcellular targets. Such an explanation cannot account, however, for the observed variations in dose-incidence relations among radiation-induced neoplasms, which remain largely unexplained. Because of the multicausal, multistage nature of carcinogenesis, and the fact that the mechanism of carcinogenic effects is not the same in all instances, some diversity of dose-incidence relationships is to be expected.

Obviously, the observed dose-incidence curves cannot all be represented by the same mathematical function. Nevertheless, the following generalizations emerge from the data: (1) a carcinogenic-induced elevation in the age-specific incidence of a particular neoplasm may or may not result in an increase in the final cumulative incidence of tumors, depending on the survival of the population at risk; (2) chemicals differ greatly in carcinogenic effectiveness, with the result that

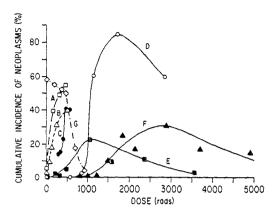
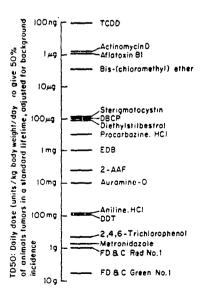


FIGURE 4. Dose-incidence curves for different neoplasms in animals exposed to external radiation: (A) myeloid leukemia in X-irradiated mice (Upton et al.⁴³); (B) mammary gland tumors at 12 months in gamma-irradiated rats (Shellabarger et al.⁴⁴); (C) thymic lymphoma in X-irradiated mice (Kaplan and Brown⁴⁵); (D) kidney tumors in X-irradiated rats (Maldague⁴⁶); (E) skin tumors in alpha-irradiated rats (percentage incidence \times 10) (Burns et al.⁴⁷); (F) skin tumors in electron-irradiated rats (percentage incidence \times 10) (Burns et al.⁴⁷); and (G) reticulum cell sarcoma in X-irradiated mice (Metalli et al.⁴⁸). (Modified from reference 49. Reproduced from Upton²¹ with permission from the Elsevier/North-Holland Publishing Company.)

the daily dose required to double the risk of neoplasia varies among different chemicals by more than six orders of magnitude (Fig. 5); (3) with ionizing radiation, the dose-incidence curve for high linear energy transfer radiation generally rises more steeply with dose and is less dependent on the dose rate than is the curve for low linear energy transfer radiation⁵⁴; (4) for many types of neoplasms, the incidence passes through a maximum at some intermediate dose and decreases with further increase in the dose (Fig. 4); (5) the median time of tumor

FIGURE 5. Range of carcinogenic potency in male rats. (Reproduced from Gold *et al.*⁵⁰ with permission from the National Institute of Environmental Health Sciences.)



$$dt^n = \text{constant} \tag{1}$$

where n is greater than one⁵⁵; (6) because radiation or a given chemical can often influence carcinogenesis through more than one mode of action, at least at high dose levels, the dose-incidence curve may reflect a combination of initiating effects, promoting effects, and anticarcinogenic effects, depending on the particular agent, dose, and exposure conditions; (7) the combined effects of different agents may be additive, synergistic, or antagonistic, depending on the agents in question and the conditions of exposure⁵⁶; (8) at low-to-moderate dose levels, the effects of a complete carcinogen can generally be accentuated by appropriate tumor-promoting stimuli, which unmask initiating effects of the carcinogen that would otherwise remain unexpressed; and (9) under conditions in which initiating

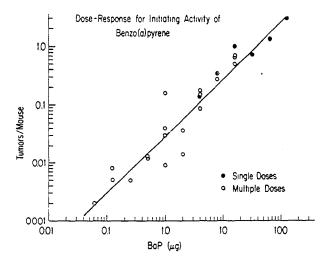
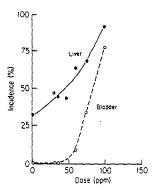


FIGURE 6. The yield of skin papillomas per mouse versus dose per application, after single and multiple doses of benzo-[a]pyrene. After treatment, 5 μg of 12-O-tetradecanoylphorbol-13-acetate was typically applied three times per week. (Reproduced from Burns and Albert⁵¹ with permission from Mary Ann Liebert, Inc.)

effects are promoted to full expression, they generally increase as a linear non-threshold function of the dose of the initiating agent (Fig. 6).

A number of experiments have been carried out with laboratory animals to characterize the dose-incidence curve in the low dose domain. In the largest of the experiments to date, performed with BALB/c female mice exposed to 2-acetylaminofluorine in the diet, the incidence of hepatomas increased as a linear nonthreshold function of the daily dose, whereas the dose-incidence curve for tumors of the urinary bladder approached a quasithreshold and resembled a hockey stick in shape (Fig. 7). Comparably large experiments have not been carried out with ionizing radiation, but the combined results of a number of sizable studies in mice, rats, and dogs imply that for most types of tumors (malignant as well as benign) the carcinogenic effectiveness per unit dose of X-rays and gamma rays is generally reduced at low doses and low dose rates, whereas that of high linear energy transfer radiations remains constant or may even be enhanced at low doses and low dose rates (Fig. 8), arguing against the likelihood of a threshold in such instances. ^{27,57,58}

FIGURE 7. Cumulative incidence of neoplasms of the liver and urinary bladder in female BALB/c mice exposed to 2-acetylaminofluorine at various concentrations in the diet for up to 33 months. (Reproduced from Littlefield *et al.*⁵²)



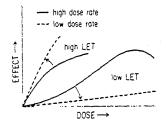
Cell Transformation in Vitro

The neoplastic transformation of cells *in vitro* is not a perfect model of carcinogenesis *in vivo*, but the two systems have enough features in common at the cellular level so that cell transformation can be exploited to identify carcinogenic agents and explore their mechanisms of action. Although few detailed dose-response curves for cell transformation have been published, the effects of benzo[a]pyrene and ionizing radiation have been studied systematically. With benzo[a]pyrene, the logarithm of the frequency of morphological transformation in Syrian hamster embryo cells increases linearly with the logarithm of the dose^{59,60}; the slope of the dose-effect curve suggests a one-hit model for this response except at the highest doses, where the deviation from linearity is attributable to cytotoxicity. A one-hit model also holds for transformation by the combined effects of X-rays and benzo[a]pyrene. 61

For Syrian hamster embryo cells transformed by X-rays, the logarithm of the transformation frequency per surviving Syrian hamster embryo cell appears to increase curvilinearly with the logarithm of the dose from 1 rad to 150 rad, but a linear response with a slope of one cannot be excluded. It is noteworthy, furthermore, that an increase in the frequency of cell transformation is detectable at a dose of only 1 rad.⁶² Dose—response curves for X-ray-induced transformation of C3H 10T1/2 cells show an exponential increase in transformation frequency (foci per surviving cell),^{63,64} with a doubling dose that is higher (about 100 rad) than the doubling dose in hamster cells (about 10 rad).

The effects of fractionating or protracting the dose of radiation vary with the experimental conditions in question. With a total dose of less than 100 rad, fractionation has been observed to enhance its transforming effectiveness, 65-67 whereas the opposite effect has been observed with higher doses (300-800 rad). 63,64,66,67 The transforming effectiveness of gamma radiation has generally

FIGURE 8. Dose-response curves depicting the incidence of tumors in laboratory animals in relation to the dose and dose rate of high and low linear energy transfer radiation. (Reproduced from Thomson et al.⁵³ [also in Updon et al.⁵⁴].)



been observed to diminish with protraction whereas that of high linear energy transfer radiation has been enhanced.⁶⁹

Few comparable split-dose experiments have been performed with chemicals. Two doses of N-acetoxy-2-fluorenylacetamine administered 2-24 hr apart, however, were observed to yield a higher frequency of transformation with Syrian hamster embryo cells than the same total dose administered at once. In contrast, methyl-N'-nitro-N-nitrosoquanidine, mitomycin C, and ultraviolet light were less effective if delivered in split doses than in a single dose. The effectiveness of methyl methanesulfonate was unaffected by dose fractionation.⁷⁰

The morphological transformation of C3H 10T1/2 cells *in vitro*, like that of cells *in vivo*, is not a one-step process. The first step appears to be rapid event, ⁷¹ occurring with one-hit kinetics in a high percentage of carcinogen-exposed cells. ^{72–74} The second step appears to be either a further qualitative change, occurring at a low frequency during the growth or confluence of the cells, ^{73–76} or an amplification of the transformed phenotype, possibly by release of the cells from inhibitory effects of neighboring nontransformed cells. ^{72,77,78} Clearly, further data will be needed to elucidate the mechanism of *in vitro* transformation and its relevance to carcinogenesis *in vivo*.

Mutations and Chromosome Aberrations

In view of the putative roles of mutations and chromosome aberrations as mechanisms of carcinogenesis, the dose-response relationships for these changes must be considered in assessing the risks associated with low-level exposure to carcinogens.

The changes in DNA that are induced by ionizing radiation and genotoxic chemicals, which include single-strand and double-strand breaks, base alterations, cross-linkage, and other modifications, can result from traversal of the cell nucleus by a single ionizing particle⁷⁹ or from interaction of the DNA with a single electrophilic molecule. 80,81 Although a dose of low linear energy transfer radiation that is lethal to 50% of dividing cells (that is, 2.5 Sv) causes hundreds of DNA strands breaks per cell, much of the damage is reparable, depending on the effectiveness of the cell's repair processes. 9 Such homeostatic repair processes are thought to enable the average cell to repair thousands of lesions in its DNA that occur "spontaneously" each day through the effects of natural background radiation, free radicals, and other degradative processes. 82,83 In spite of repair, however, the persistence of residual damage or the occurrence of lesions resulting from misrepair can give rise to mutations or chromosome aberrations or both, the frequency of which will depend on the amount and severity of DNA damage.

The frequency of mutations at the guanine (hypoxanthine) phosphoribosyl transferase locus in human lymphocytes increases as a linear, nonthreshold function of the X-ray dose over the range from 50 to 220 mSv, amounting to about six mutations per 10⁶ cells per Gy, whether the dose is delivered in several fractionated exposures or in a single brief exposure.⁸⁴

In X-irradiated mouse spermatogonia in vivo, the frequency of specific locus mutations increases as a linear-quadratic function of the dose, amounting to approximately six mutations per 10⁶ cells per locus per Sv at low-to-intermediate doses and dose rates; with fast neutrons, the frequency of mutations increases more steeply, as a linear nonthreshold function of the dose, and independent of the dose rate.⁵⁶

The frequency of chromosomal aberrations in human lymphocytes irradiated in vitro increases as a linear-quadratic nonthreshold function of the dose, approximating 0.1 aberration per cell per Sv in the low-to-intermediate dose region. The dose required to double the frequency of aberrations in such cells can thus be calculated to approximate 0.05 Sv. With high linear energy transfer radiation, the frequency of aberrations increases more steeply, as a linear nonthreshold function of the dose, and irrespective of the dose rate. 56,86

Dose-response relationships for chemically induced mutations and chromosomal aberrations are less well defined than those for ionizing radiation, in part because of the greater diversity of types and mechanisms of chemically induced DNA damage. Chemical mutagenesis and clastogenesis involve complex processes, including pharmacokinetic variables (uptake, transport, distribution, and excretion), metabolic activation and detoxication, and various reactions leading to the production of DNA lesions and their subsequent repair-misrepair. Each of these steps may conceivably involve first-order kinetics at low doses and hence be linear, so that in principle the overall process may be linear and not approach a threshold. Even if mutagenesis at low dose levels involved only linear processes, the slope of the resulting dose-response relationship could be orders of magnitude shallower than the slope at high dose levels, so that the dose-response curve could appear to reach a threshold or a quasithreshold. 87 In fact, nonlinear mechanisms are likely to operate in at least some of the transport, metabolism, elimination, and repair processes that are involved in mutagenesis, 87 and it is noteworthy that a single step involving a threshold in such a sequence could give the overall process a threshold. Hence, in view of the complexity of the many processes involved in chemical mutagenesis, it is not astonishing that the dose-response curves for mammalian cells exposed in vitro have been observed to include responses that appear to involve linear nonthresholds as well as quasithresholds.88 Whether any of the responses truly involves a threshold, however, cannot be determined from existing data.

Other factors complicating assessment of the practical implications of dose-response data for chemical mutagenesis are the fact that chemicals vary more than a millionfold in mutagenic potency and the fact that the magnitude of the variation among chemicals also differs depending on the types of cells and indices of mutagenicity in question. 88,89

FACTORS MODIFYING THE DOSE RESPONSE

A variety of factors are known to affect dose-incidence relationships in carcinogenesis. 90 These include, among others, variables influencing the susceptibility of exposed individuals (for example, genetic background, 11 age at exposure, 28 immunological reactivity, 91 differences in DNA repair capacity, 85 and differences in drug metabolism 92,93). The capacity to metabolize a chemical can vary among humans by more than 100-fold 94 and among species by more than 1000-fold. 93 In any one person, moreover, the balance between toxification and detoxification may be highly dose-dependent. 95 As a result, the effective dose of a substance to its biological target may differ substantially among persons at a given ambient exposure level.

Also of potential importance in modifying the dose-response relationship for a given carcinogen are the effects of other physical or chemical agents. The interac-

tive effects of these agents may be additive, synergistic, or inhibitory, depending on the agents in question and the conditions of exposure. ^{56,96} In a number of instances, appropriate stimulation by a tumor-promoting agent has been observed to convert a curvilinear dose-incidence response involving a threshold into a linear response not involving a threshold (Fig. 9).

HEALTH POLICY IMPLICATIONS

The problem of risk assessment for purposes of public health policy is complicated by the fact that cancer arises through successive stages, each of which may be affected differently and in as yet unpredictable ways by a given agent. No single process is known to be applicable to all carcinogens, all types of cancer, and all persons at risk. Most multistage models assume, however, that 1) a normal cell must undergo two or more stochastic and essentially irreversible changes to become transformed into a cancer cell; 2) one or more of the changes may be inherited via the fertilized egg (zygote); and 3) it is the clonal proliferation of a

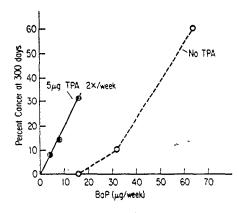


FIGURE 9. The incidence of carcinomas of the skin after 350 days of treatment in mice exposed to a weekly dose of benzo[a]pyrene on Monday, with or without 5.0 μ g of 12-O-tetradecanoylphorbol-13-acetate on Wednesday and Friday. Doses refer to the amount of benzo[a]pyrene given per week. The treatments were started at 56 days of age. (Reproduced from Burns and Albert⁵¹ with permission from Mary Ann Liebert, Inc.)

single cell in which all the necessary changes have occurred that ultimately gives rise to a cancer. ⁹⁷ According to such a model, any agent that directly or indirectly increases the probability of any one of the changes may be a carcinogen because such an agent would increase the likelihood that a cell will ultimately acquire all of the changes necessary for transformation. The model also implies that the changes necessary for malignant transformation must occur in the proper sequence, because some carcinogenic stimuli act only on early stages while others act on later stages, and that carcinogens that affect different stages in the process can be multiplicative rather than merely additive in their combined effects.

In the absence of definitive human data, risk assessment must depend on other types of evidence (for example, on the results of bioassays in laboratory animals or on short-term tests for carcinogenicity). Under such circumstances, risk assessment is complicated by questions about 1) the reliability of the test system for predicting risks to humans (quantitatively as well as qualitatively); 2) the reproducibility of the test results; 3) the influence of species differences in pharmacokinetics, metabolism, hoemostasis, repair rates, life span, organ sensitivity, and baseline cancer rates; 4) the influence of differences in dose, dose rate, and routes

of exposure; 5) the significance of benign, as opposed to malignant, tumors; 6) the precise nature of the dose-incidence relationship; and 7) the significance of negative results.

On the basis of present knowledge, the carcinogenicity of an agent for human tissue cannot be predicted accurately by extrapolation from animal data. A chemical that causes tumors in a particular organ of one species may cause tumors in another organ, or no tumors at all, in other species; for example, bioassay results in the mouse have been predictive for the rat in only about 80% of cases, and vice versa. 98,99 The problem is complicated further by the fact that the human population is exposed to myriads of agents interacting in various ways, whereas animals in the standard bioassay are ordinarily exposed to only one agent at a time.

The dose-incidence models used by national and international experts for estimating the carcinogenic risks of low-level ionizing radiation are generally of the nonthreshold type. ^{27-29,100} The models also allow, however, for the fact that the magnitude of risk per unit dose appears to vary with the form of cancer, sex, age at irradiation, type of radiation (linear energy transfer), dose, and dose rate. In view of these differences, each type of neoplasm is generally considered individually, with efforts to integrate insofar as possible all relevant epidemiological and experimental data.

Although the relation between incidence and radiation dose is known to vary from one type of neoplasm to another, the observed effects of dose rate and linear energy transfer on the dose-incidence relation generally conform to the patterns illustrated in FIGURE 8, which are consistent with those expected if one were to assume that carcinogenesis could be initiated in a suitably susceptible individual by a mutation or chromosomal aberration in a single somatic cell. According to this interpretation, the dose-incidence curve for high linear energy transfer radiation would be expected to conform, in general, to the expression

$$I = C + aDE^{-pD} (2)$$

where I is the incidence at dose D, C is the incidence in nonirradiated controls, and a and p are constant coefficients; for low linear energy transfer radiation, the dose-incidence curve would conform, in general, to the expression

$$I = (C + aD + bD^2)e - (pD + qD^2)$$
 (3)

where the symbols are comparable to those above, except for different values of the coefficients a and p and an additional coefficient q. 101

Although many of the observed dose-incidence curves conform to the patterns described above, the curve for breast cancer appears more nearly linear, and the curve for osteosarcomas induced by radium-226 appears more nearly quadratic. Because of the complex, multicausal, multistage nature of carcinogenesis, no one simple model is likely to characterize the dose-incidence relation over a wide range of doses and exposure conditions. At intermediate-to-high doses, a complete carcinogen can be expected to exert promoting effects as well as initiating effects on tumor formation through alterations in cell population kinetics and other changes. At still higher doses, the response can be expected to saturate because of cytotoxicity.

In view of uncertainty about the shape of the dose-incidence curve at low doses and low dose rates, various hypothetical models have been used in an effort to arrive at a range of estimates for assessing the risks of low-level radiation (Fig. 10) and chemicals (Fig. 11).



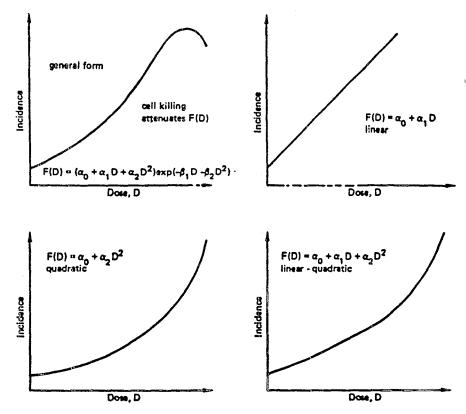


FIGURE 10. Dose-response curves for four different mathematical models relating cancer incidence to radiation dose. (Reproduced from Reference 28 with permission from the National Academy Press.)

Criteria to aid in the evaluation of epidemiological and experimental data on the carcinogenicity of chemicals have been formulated by the International Agency for Research on Cancer, ²⁶ the Interagency Regulatory Liaison Group, ¹⁰² and the Office of Science and Technology Policy. ¹⁰³ These criteria include definitions for weighing the adequacy of the data (for example, definitions of "sufficient evidence" and "limited evidence" ²⁶). In situations where there is sufficient evidence for the carcinogenicity of a chemical in laboratory animals but not in humans, the compound is assumed to present a carcinogenic risk to humans, although the magnitude of the risk cannot be estimated with precision. ²⁶ Although bioassay and short-term "screening" tests may give information on the mode of action of a chemical, such tests are considered to provide no more than supporting evidence of carcinogenicity and not to provide sufficient evidence by themselves.

Estimation of carcinogenic risks on the basis of animal data, however good the animal data may be, is fraught with uncertainty. Although a chemical with carcinogenic potency in one species (such as aflatoxin B₁) is likely to be carcinogenic in another, the procedure for extrapolating across species involves assumptions about species differences in metabolism and appropriate scaling factors for dose and time. Various attempts have been made to determine correct scaling factors based on pharmacokinetic data, 95 but the question remains unresolved.

In addition, a dose-response model must be used for interpolating between the lowest dose at which a significantly increased incidence has been observed and the baseline (zero dose) incidence. For this purpose, a linear, nonthreshold (one-hit) dose-incidence model is generally recommended, although such a model cannot be verified experimentally. 104 This type of model gives higher estimates, however, than other models (Fig. 10 and Table 2). Hence it is usually thought likely to overestimate the risk at low doses and is thus often considered to estimate the "upper limit" of risk.

Evidence concerning the modes of action of different classes of carcinogens (initiators, promoters, co-carcinogens, and complete carcinogens) suggests that a linear nonthreshold model may be appropriate only for initiating agents and complete carcinogens, whereas models yielding smaller estimates of risks at low doses might represent more accurately the dose-incidence relationships for other classes of carcinogens. For some types of carcinogens, thresholds might even be envisioned to exist because of relevant pharmacokinetic factors. For example, some chemicals that must be activated metabolically to become carcinogenic may be handled through nonlinear metabolic processes, with the result that thresholds for their carcinogenic effects may exist. For addition, some agents may act through toxic or systemic effects that are produced only at high doses (for example, those causing carcinogenic effects on the mucosa of the urinary bladder in association with cystitis and urinary tract calculi, for those acting through immunosuppressive effects.

If it can be shown, however, that a chemical acts through mechanisms that are shared by agents that contribute to the baseline incidence of "spontaneously

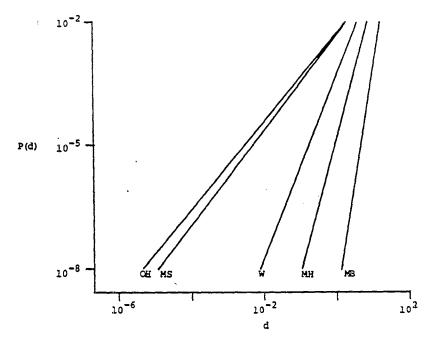


FIGURE 11. Estimated risk of liver cancer, P(d), in relation to dose of aflatoxin, d, as determined with different dose-incidence models. The models for the different curves are as follows: OH, one-hit model; MS, multistage model; W, Weibull model; MH, multihit model; MB, Mantel-Bryan (log-probit model). (Reproduced from Krewski and Van Ryzin¹⁰⁴ with permission from the Elsevier/North-Holland Publishing Company.)

TABLE 2. Estimated Human Risks from Ingestion of 0.12 G/Day of Saccharin

| Method of High- to Low-Dose Extrapolation | Lifetime Cases per Million Exposed | Cases per 50 Million per Year | |
|--|--|-------------------------------------|--|
| Rat dose adjusted to human dose by surface | | | |
| area rule | | | |
| Single-hit model | 1,200 | 840 | |
| Multistage model (with quadratic term) | 5 | 3.5 | |
| Multihit model | 0.001 | 0.0007 | |
| Mantel-Bryan probit model | 450 | 315 | |
| Rat dose adjusted to human dose by mg/kg/day | | | |
| equivalence | | | |
| Single-hit model | 210 | 147 | |
| Multihit model | 0.001 | 0.0007 | |
| Mantel-Bryan probit model | 21 | 14.7 | |
| Rat dose adjusted to human dose by mg/kg/ | | | |
| lifetime equivalence | | | |
| Single-hit model | 5,200 | 3,640 | |
| Multihit model | 0.001 | 0.0007 | |
| Mantel-Bryan probit model | 4,200 | 2,940 | |

Note: Adapted from Reference 105.

occurring" cancer, then exposure to only a small dose of the chemical can be expected to increase the incidence by some finite amount. For this reason, the use of a nonthreshold model is generally recommended in risk assessment when the mode of action of the carcinogen in question is not known.

CONCLUSIONS

The possibility that there may be no threshold for the induction of some forms of cancer by ionizing radiation or certain chemicals, at least in appropriately susceptible individuals, is suggested by (1) evidence that most cancers arise from a single transformed cell; (2) the heritable nature of the transformed phenotype; (3) the association between neoplastic transformation and specific mutations or chromosomal aberrations; (4) the correlation between carcinogenicity and genotoxicity; (5) the nature of the observed dose—response relationships for mutations, chromosomal aberrations, and cell transformation in vitro; and (6) the nature of the dose—incidence relationships for certain neoplastic lesions in vivo.

At the same time, however, carcinogenesis appears to be a multistage process involving the stepwise evolution of increasingly autonomous cells in which the outcome is influenced by such variables as age, genetic constitution, physiological state, metabolism, and homeostatic interactions within and among tumor-forming cells and normal cells. Other variables that complicate analysis of dose-incidence relationships are (1) poorly defined interactions among cancer-causing agents, which may be additive, multiplicative, or antagonistic in their combined effects; (2) the fact that the human environment contains myriads of agents, many of which are known to modulate the effects of others; (3) the existence of nonlinear kinetics in the metabolism of certain chemical carcinogens; and (4) evidence that some agents act primarily through mechanisms that presumably operate only at high dose levels.

Because of the complexity of carcinogenesis and the variability of dose-incidence relationships, it is not possible on the basis of present knowledge to extrapolate confidently across different species, population groups, doses, and conditions of exposure in estimating the carcinogenic risks of a particular carcinogen for human populations exposed at low dose levels. Agents differ widely in metabolism, potency, and mode of action, with the result that their hazards can be expected to vary greatly at low doses, whether estimated with the use of a threshold dose-incidence model or a nonthreshold dose-incidence model. In selecting the appropriate dose-incidence model for risk assessment, one must consider each agent individually, taking all relevant epidemiological, clinical, and experimental data into account.

The existing evidence does not rigorously exclude a threshold for any carcinogen, but the use of a nonthreshold model for ionizing radiation and most chemicals, especially those with genotoxic activity, is generally recommended on the basis of present knowledge. The choice of a threshold model cannot be justified in the absence of evidence that the metabolism or mode of action or both of the agent varies appropriately in relation to the dose.

REFERENCES

- MULLER, H. J. 1954. The manner of production of mutations by radiation. In Radiation Biology. Vol. 1: High-Energy Radiation. A. Hollaender, Ed.: 475-626. McGraw-Hill. New York, NY.
- SCHERER, E. & P. EMMELOT. 1979. Multihit kinetics of tumor cell formation and risk assessment of low doses of carcinogen. In Carcinogens: Identification and Mechanisms of Action. A. C. Griffin & C. R. Shaw, Eds.: 337-364. Raven Press. New York, NY.
- FIALKOW, P. J. 1977. Clonal origin of human tumors. Biochim. Biophys. Acta 458: 283-321.
- IANNACCONE, P. M., R. L. GARDNER & H. HARRIS. 1978. The cellular origin of chemically induced tumors. J. Cell Sci. 29: 249-269.
- 5. PONDER, B. A. J. 1980. Genetics and cancer. Biochim. Biophys. Acta 605: 368-410.
- SANDBERG, A. A. 1983. A chromosomal hypothesis of oncogenesis. Cancer Genet. Cytogenet. 8: 277-285.
- 7. FARBER, E. 1984. Cellular biochemistry of the stepwise development of cancer with chemicals. G. H. A. Clowes Memorial Lecture. Cancer Res. 44: 5463-5474.
- 8. Bertram, J. S. & C. Heidelberger. 1974. Cell cyclic dependency of oncogenic transformation induced by N-methyl-N'-nitro-N-nitrosoguanidine in culture. Cancer Res. 34: 526-537.
- 9. BATES, R. R., S. A. EATON, D. L. MORGAN & S. YUSPA. 1970. Replication of DNA after binding of the carcinogen 7-dimethylbenz[a]anthracene. J. Natl. Cancer Inst. 45: 1223-1228.
- KAKUNAGA, T. 1974. Requirement for cell replication in the fixation and expression of the transformed state in mouse cells treated with 4-nitroquinoline-1-oxide. Int. J. Cancer 14: 736-742.
- KNUDSON, A. G. 1985. Hereditary cancer, oncogenes, and antioncogenes. Cancer Res. 45: 1437.
- 12. Huberman, E., R. Mager & L. Sachs. 1976. Mutagenesis and transformation of normal cells by chemical carcinogenesis. Nature 204: 360-361.
- PARODI, S. & G. BRAMBILLA. 1977. Relationship between mutation and transformation frequencies in mammalian cells treated in vitro with chemical carcinogens. Mutat. Res. 47: 53-74.
- BARRETT, J. C., B. D. CRAWFORD & P. O. P. Ts'o. 1980. The role of somatic mutation in a multistage model of carcinogenesis. In Mammalian Cell Transforma-

- tion by Chemical Carcinogens. N. Mishra, V. C. Dunkel & M. Mehlman, Eds.: 467. Senate Press. NJ.
- LAND, H., L. F. PARADA & R. A. WEINBERG. 1983. Cellular oncogenes and multistep carcinogenesis. Science 222: 771-778.
- 16. Blumberg, P. M. 1980, 1981. In vitro studies on the mode of action of the phorbol esters, potent tumor promoters, Parts 1 and 2. CRC Crit. Rev. Toxicol 3: 152-234.
- 17. Blumberg, P. M., S. Jaken, B. Konig, N. Sharkey, K. Leach, A. Jeng & E. Yeh. 1984. Mechanisms of action of the phorbol ester tumor promoters: Specific receptors for lipophilic ligands. Biochem. Pharmacol. 33: 933-940.
- Weinstein, I. B., S. Gatto-Celli, P. Kirschmeier, W. Hsiao & A. Jeffrey. 1984. Cellular targets and host genes in multistage carcinogenesis. Fed. Proc. 43: 2287-2294.
- Weinstein, I. B. 1985. Cell culture studies on the mechanism of action of chemical carcinogens and tumor promoters. In Carcinogenesis: A Comprehensive Survey. Vol. 10: The Role of Chemicals and Radiation in the Etiology of Cancer. E. Huberman & S. H. Barr, Eds.: 177-187. Raven Press. New York, NY.
- 20. VAN DUUREN, B. L. 1976. Tumor-promoting and co-carcinogenic agent in chemical carcinogenesis. *In* Chemical Carcinogens. C. E. Searle, Ed.: 24-51. American Chemical Society. Washington, DC.
- UPTON, A. C., D. G. CLAYSON, D. JANSEN, H. ROSENKRANZ & G. WILLIAMS. 1984. Report of ICPEMC task group on the differentiation between genotoxic and non-genotoxic carcinogens. Mutat. Res. 133: 1-49.
- 22. CERUTTI, P. A., P. AMSTAD & I. EMERIT. 1983. Tumor promoter phorbol myristate acetate-induced membrane-mediated chromosomal damage. *In* Radioprotectors and Anticarcinogens. O. F. Nygaard & M. G. Simic, Eds.: Academic Press. New York, NY.
- 23. TROLL, W. & R. WEISNER. 1985. The role of oxygen radicals as a possible mechanism of tumor promotion. Annu. Rev. Pharmacol. Toxicol. 25: 509.
- LIEHR, J. G., K. RANDERATH & E. RANDERATH. 1985. Target organ-specific covalent DNA damage preceding diethylstilbestrol-induced carcinogenesis. Carcinogenesis 6: 1067-1069.
- 25. FOULDS, L. 1969. Neoplastic Development. Vol. 1. Academic Press. New York, NY.
- 26. International Agency for Research on Cancer. (1982). IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans: Chemicals, Industrial Processes, and Industries Associated with Cancer in Humans. Supplement 4. International Agency for Research on Cancer. Lyons.
- United Nations Scientific Committee on the Effects of Atomic Radiation. 1977.
 Sources and Effects of Ionizing Radiation. Report to the General Assembly, with Annexes. United Nations. New York, NY.
- National Academy of Sciences, Advisory Committee on the Biological Effects of Ionizing Radiation. 1980. The Effects on Populations of Exposure to Low Levels of Ionizing Radiation. National Academy of Science. Washington, DC.
- 29. RALL, J. E., G. W. BEEBE, D. G. HOEL, S. JABLON, C. E. LAND, O. F. MYGAARD, A. C. UPTON, R. S. YALOW & V. H. ZEVE. 1985. Report of the National Institutes of Health Working Group to Develop Radioepidemiological Tables. U.S. National Institutes of Health Publication 85-2748. Washington, DC.
- Monson, R. P. & B. MacMahon. 1984. Prenatal X-ray exposure and cancer in children. In Radiation Carcinogenesis: Epidemiology and Biological Significance. J. D. Boice, Jr. & J. F. Fraumeni, Jr., Eds.: 97-105. Raven Press. New York, NY.
- 31. HARVEY, E. B., J. D. BOICE, JR., M. HONEYMAN & J. T. FLANNERY. 1985. Prenatal X-ray exposure and childhood cancer in twins. N. Eng. J. Med. 312: 541-545.
- 32. Modan, B., E. Ron & A. Werner. 1977. Thyroid cancer following scalp irradiation. Radiology 123: 741-744.
- 33. Shore, R. E., E. D. Woodard, L. H. Hemplemann & B. S. Pasternack. 1980. Syngerism between radiation and other risk factors for breast cancer. Prev. Med. 9: 815-822.
- 34. BOICE, J. D., JR., C. E. LAND, R. E. SHORE, J. E. NORMAN & M. TOKUNAGA. 1979. Risk of breast cancer following low-dose exposure. Radiology 131: 589-597.

- 35. DOLL, R. 1978. An epidemiological perspective of the biology of cancer. Cancer Res. 38: 3573-3583.
- 36. DOLL, R. & R. PETO. 1981. The causes of cancer: Quantitative estimates of avoidable risk of cancer in the United States today. J. Natl. Cancer Inst. 66: 1192-1308.
- 37. SAFFIOTTI, U. 1973. Metabolic host factors in carcinogenesis. *In* Host Environment Interactions in the Etiology of Cancer in Man. R. Doll, I. Vodopija & W. Davis, Eds.: 243-252. International Agency for Research on Cancer. Lyons.
- 38. WILLIAMS, M. H. C. 1958. Occupational tumors of the bladder. *În* Cancer. R. W. Raven, Ed.: 337–380. Butterworth. London.
- 39. NICHOLSON, W. J. 1985. Airborne Asbestos Health Assessment Update. U.S. Environmental Protection Agency Publication 600/8-84-003F. Washington, DC.
- SELIKOFF, I. J. 1981. Constraints in estimating occupational contributions to current cancer mortality in the United States. In Banbury Report 9: Quantification of Occupational Cancer. R. Peto & M. Schneiderman, Eds.: 3-13. Cold Spring Harbor Laboratory. Cold Spring Harbor. New York, NY.
- 41. DOLL, R. 1970. Cancer and aging: The epidemiologic evidence. Oncology 5: 1-28.
- 42. HAMMOND, E. C., I. J. SELIKOFF & H. SEIDMAN. 1979. Asbestos exposure, cigarette smoking and death rates. Ann. N.Y. Acad. Sci. 330: 473-490.
- UPTON, A. C., F. F. WOLFF, J. FURTH & A. W. KIMBALL. 1958. A comparison of the induction of myeloid and lymphoid leukemias in X-irradiated RF mice. Cancer Res. 18: 842–848.
- 44. Shellabarger, C. J., V. P. Bond, E. P. Cronkite & G. E. Aponte. 1969. Relationship of dose to total-body ⁶⁰Co radiation to incidence of mammary neoplasia in female rats. *In* Radiation-Induced Cancer: 161−172. IAEA. Vienna.
- KAPLAN, H. S. & M. B. BROWN. 1952. A quantitative dose-response study of lymphoid tumor development in irradiated C57 black mice. J. Natl. Cancer Inst. 13: 185-208.
- MALDAGUE, P. 1969. Comparative study of experimentally induced cancer of the kidney in mice and rats with X-rays. In Radiation-Induced Cancer: 439-458. International Atomic Energy Agency. Vienna.
- 47. Burns, F., R. E. Albert & R. D. Heimbach. 1968. RBE for skin tumors and hair follicle damage in the rat following irradiation with alpha particles and electrons. Radiat. Res. 36: 225-241.
- METALLI, P., V. COVELLI, M. DIPAOLA & G. SILINI. 1974. Dose-incidence data for mouse reticulum cell sarcoma. Radiat. Res. 59: 21.
- United Nations Scientific Committee on the Effects of Atomic Radiation. 1972. Ionizing Radiation: Levels and Effects. Report to the General Assembly, Official Records, 27th Session, Supplement Number 25 (A/8725). United Nations. New York, NY.
- 50. GOLD, L. S., C. B. SAWYER, M. MAGAW, et al. 1984. A carcinogenic potency database of the standardized results of animal bioassays. Environ. Health Perspect. 58: 0...310
- 51. Burns, F. J. & R. E. Albert. 1982. Mouse skin papillomas as early stages of carcinogenesis. J. Am. Coll. Toxicol. 1: 29-45.
- 52. LITTLEFIELD, N. A., J. H. FARMER & D. W. GAYLOR. 1979. Effects of dose and time in a long-term, low-dose carcinogenic study. J. Environ. Pathol. Toxicol. 3: 17-34.
- THOMSON, J. F., L. S. LOMBARD, D. GRAHN, F. S. WILLIAMSON & T. F. FRITZ. 1982. RBE of fission neutrons for life shortening and tumorigenesis. In Neutron Carcinogenesis. J. J. Broerse & G. B. Gerber, Eds.: 75-94. Commission of the European Communities. Luxembourg.
- UPTON, A. C. 1984. Biological aspects of radiation carcinogenesis. In Radiation Carcinogenesis: Epidemiology and Biological Significance. J. D. Boice, Jr. & J. F. Fraumeni, Jr., Eds.: 9-19. Raven Press. New York, NY.
- ALBERT, R. E. & B. ALTSHULER. 1973. Consideration relating to the formulation of limits for unavoidable population exposures to environmental carcinogens. In Radionuclide Carcinogenesis. C. L. Sanders, R. H. Bresch, J. E. Ballon & D. D. Mahlum, Eds.: 233. U.S. Atomic Energy Commission. Washington, DC.
- 56. United Nations Scientific Committee on the Effects of Atomic Radiation. 1982. Ioniz-

- ing Radiation: Sources and Biological Effects. Report to the General Assembly, with Annexes. United Nations, New York, NY.
- 57. Broerse, J. J. & G. B. Gerber, Eds. 1982. Neutron Carcinogenesis. Commission of the European Communities. Luxembourg.
- UPTON, A. C. 1985. Biological basis for assessing carcinogenic risks of low-level radiation. In Carcinogenesis: A Comprehensive Survey. Vol. 10: The Role of Chemicals and Radiation in the Etiology of Cancer. E. Huberman & S. H. Barr, Eds.: 381-401. Raven Press. New York, NY.
- HUBERMAN, E. & L. SACHS. 1966. Cell susceptibility to transformation and cytotoxicity by the carcinogenic hydrocarbon benzo[a]pyrene. Proc. Natl. Acad. Sci. USA 56: 1123-1129.
- DIPAOLO, J. A., P. J. DONOVAN & R. L. NELSON. 1971. In vitro transformation of hamster cells by polycyclic hydrocarbons: Factors influencing the number of cells transformed. Nature (London), New Biol. 230: 240-242.
- 61. GART, J. J., J. A. DIPAOLO & P. J. DONOVAN. 1979. Mathematical models and the statistical analyses of cell transformation experiments. Cancer Res. 39: 6069-6075.
- 62. Borek, C. & E. J. Hall. 1973. Transformation of mammalian cells in vitro by low doses of X-rays. Nature 243: 450-453.
- 63. Terzaghi, M. & J. B. Little. 1976. X-radiation-induced transformation in a C3H mouse embryo-derived cell line. Cancer Res. 36: 1367-1374.
- HAN, A. & M. M. ELKIND. 1979. Transformation of mouse C3H/10T1/2 cells by single and fractionated doses of X-rays and fission-spectrum neutrons. Cancer Res. 39: 123-130.
- BOREK, C. & E. J. HALL. 1974. Effect of split doses of X-rays on neoplastic transformation of single cells. Nature 252: 499-501.
- 66. MILLER, A. & E. J. HALL. 1978. X-ray-dose fractionation and oncogenic formations in cultured mouse embryo cells. Nature 272: 58-60.
- 67. MILLER, R. C., E. J. HALL & H. H. Rossi. 1979. Oncogenic transformation in mammalian cells *in vitro* with split doses of X-rays. Proc. Natl. Acad. Sci. USA 76: 5755-5758.
- 68. TERZAGHI, M. & J. B. LITTLE. 1976. Oncogenic transformation in vitro after split-dose X-irradiation. Int. J. Radiat. Biol. 29: 583-587.
- 69. HILL, C. K., A. HAN & M. M. ELKIND. 1984. Fission-spectrum neutrons at low dose rate enhance neoplastic transformation in the linear, low dose region (0–10 Gy). Int. J. Radiat. Biol. 46: 11.
- 70. POPESCU, N. C., S. C. AMSBAUGH & J. A. DIPAOLA. 1984. Correlation of morphological transformation to sister chromatid exchange induced by split doses or chemical or physical carcinogens on cultured Syrian hamster cells. Cancer Res. 44: 1933-
- BACKER, J. M., M. BOERZIG & I. B. WEINSTEIN. 1982. When do carcinogen-treated 19T1/2 cells acquire the commitment for forming transformed foci? Nature 299: 458-460.
- 72. HABER, D. A. & W. G. THILLY. 1978. Morphological transformation of C3H 10T1/2 cells subcultured at low densities. Life Sci. 22: 1663-1674.
- 73. FERNANDEZ, A., S. MONDAL & C. HEIDELBERGER. 1980. Probabilistic view of the transformation of cultured C3H 10T mouse embryo fibroblasts by 3-methylcholan-threne. Proc. Natl. Acad. Sci. USA 77: 7272-7276.
- 74. Kennedy, A. R. & J. B. Little. 1984. Evidence that a second event in X-ray-induced oncogenic transformation in vitro occurs during cellular proliferation. Radiat. Res. 99: 228-248.
- 75. Kennedy, A. R., J. Cairns & J. B. Little. 1984. Timing of the steps in transformation of C3H 10T1/2 cells by X-irradiation. Nature 307: 85-87.
- 76. BARRETT, J. C. & E. ELMORE. 1984. Comparison of carcinogenesis and mutagenesis of mammalian cells in culture. *In* Handbook of Experimental Pharmacology. L. S. Andrews, R. J. Lorentzen & W. D. Flamm, Eds.: 171-206. Springer-Verlag. Berlin.
- 77. MORDAN, L. J., J. E. MARTNER & J. S. BERTRAM. 1983. Quantitative neoplastic transformation of C3H/10T1/2 fibroblasts: Dependence upon the size of the initiated cell colony at confluence. Cancer Res. 43: 4062-4067.

- BERTRAM, J. S. & J. E. MARTNER. 1985. Quantitative neoplastic transformation in C3H/10T1/2 cells. In Assessment of Risk from Low-Level Exposure to Radiation and Chemicals. A. D. Woodhead, C. J. Shellbarger, V. Pond & A. Hollander, Eds.: 205-222. Plenum. New York, NY.
- COLE, A., R. E. MEYN, R. CHEN, P. M. CORRY & W. HITTELMAN. 1980. Mechanisms of cell injury. In Radiation Biology in Cancer Research. R. E. Meyn & H. R. Withers, Eds.: 33-58. Raven Press. New York, NY.
- 80. SINCER, B. & J. T. KUSMIEREK. 1982. Chemical mutagenesis. Annu. Rev. Biochem. 51: 655-693.
- 81. SINGER, B. & D. GRUNBERGER. 1983. Molecular Biology of Mutagens and Carcinogens. Plenum. New York, NY.
- SHAPIRO, R. 1981. Damage to DNA caused by hydrolysis. In Chromosome Damage and Repair. E. Seeberg & K. Kleppe, Eds.: 3-18. Plenum. New York, NY.
- 83. SAUL, R. L. & B. N. AMES. 1985. Background levels of DNA damage in the population. *In Damage and Repair: Implications for Risk Assessment. M. Simic*, L. Grossman & A. C. Upton, Eds.: 529-535. Plenum. New York, NY.
- 84. GROSOVSKY, A. J. & J. B. LITTLE. 1985. Evidence for linear response for the induction of mutations in human cells by X-ray exposure below 10 rads. Proc. Natl. Acad. Sci. USA 82: 2092-2095.
- 85. National Council on Radiation Protection and Measurements. 1980. Influence of Dose and Its Distribution in Time on Dose-Response Relationships for Low-LET Radiations. National Council on Radiation Protection and Measurements Report 64. Washington, DC.
- LLOYD, D. C. & R. J. PURROTT. 1981. Chromosome aberration analysis in radiological protection dosimetry. Radiat. Prot. Dosimetry 1: 19-28.
- 87. Hoel, D. G., N. L. Kaplan & M. W. Anderson. 1983. Implication of nonlinear kinetics on risk estimation in carcinogenesis. Science 219: 1023-1037.
- 88. EHLING, U. H., D. AVERBECK, P. A. CERUTTI, J. FRIEDMAN, H. GRIEM, A. C. KOLBYE, JR. & M. L. MENDELSOHN. 1983. Review of the evidence for the presence or absence of thresholds in the induction of genetic effects by genotoxic chemicals. International Commission for Protection Against Environmental Mutagens and Carcinogens Publication 10. Mutat. Res. 123: 281-341.
- National Academy of Sciences/National Research Council. 1982. Identifying and Estimating the Genetic Impact of Chemical Mutagens. National Academy of Sciences. Washington, DC.
- STARR. T. B. 1985. The role of mechanistic data in dose-response modeling. In
 Assessment of Risk from Low-Level Exposure to Radiation and Chemicals. A. D.
 Woodhead, C. J. Shellbarger, V. Pond & A. Hollaender, Eds.: 101-124. Plenum.
 New York, NY.
- 91. OLD, L. J. 1981. Cancer immunology: The search for specificity. G. H. A. Clowes Memorial Lecture. Cancer Res. 41: 361.
- 92. Mommsen, S., N. M. Barford & J. Aagaard. 1985. N-Acetyltransferase phenotype in the urinary bladder carcinogenesis of a low-risk population. Carcinogenesis 6: 199-201.
- 93. Nebert, D. W. & F. J. Gonzalez. 1985. Cytochrome P-450 gene expression and regulation. Trends Pharmacol. Sci. 6: 160-164.
- 94. GOLDSTEIN, A., L. AORNOW & S. M. KALMAN. 1974. Principles of Drug Action: The Basis of Pharmacology. 2nd edit. John Wiley & Sons. New York, NY.
- 95. DIETZ, E. K., J. C. RAMSEY & P. G. WATANABE. 1983. Experimental studies to human risk. Environ. Health Perspect. 52: 9-14.
- 96. UPTON, A. C. 1982. Principles of tumor biology, etiology, and prevention. *In Principles and Practices of Oncology*. V. T. DeVita, S. Hellman & S. A. Rosenberg, Eds.: 33. J. B. Lippincott. Philadelphia, PA.
- 97. WHITTEMORE, A. S. 1978. Quantitative theories of carcinogenesis. Adv. Cancer Res. 27: 55-88.
- 98. Purchase, I. F. H. 1982. An appraisal of predictive tests for carcinogenicity. Mutat. Res. 99: 53-71.

- HASEMAN, J. K. 1984. Statistical issues in the design, analysis, and interpretation of animal carcinogenicity studies. Environ. Health Perspect. 58: 385-392.
- International Commission on Radiological Protection. 1977. Recommendations of the International Commission on Radiological Protection. ICRP Publication 26, Annals of the ICRP, Vol. 1, No. 3. Pergamon Press. Oxford.
- UPTON, A. C. 1977. Radiobiological effects of low doses: Implications for radiological protection. Radiat. Res. 71: 51-74.
- Interagency Regulatory Liaison Group. 1979. Work group on risk assessment: Scientific bases for identification of potential carcinogens and estimation. J. Natl. Cancer. Inst. 63: 241-268.
- 103. OFFICE OF SCIENCE AND TECHNOLOGY POLICY. 1985. Chemical Carcinogens; A Review of the Science and Its Associated Principles. February 1985, Federal Register Vol. 50, No. 50, Thursday, March 14,: 10372-10442.
- 104. KREWSKI, B. & J. VAN RYZIN. 1981. Dose-response models for quantal response toxicity data. In Statistics and Related Topics. J. Sxorgo, D. Dawson, J. N. K. Rao & E. Saleh, Eds.: 201-231. Elsevier/North-Holland. New York, NY.
- 105. NATIONAL ACADEMY OF SCIENCES. 1978. Saccharin: Technical Assessment of Risks and Benefits. Part 1 of 1 2-Part Study of the Committee for a Study on Saccharin and Food Safety Policy. Panel I: Saccharin and Its Impurities. Assembly of Life Sciences/National Research Council and the Institute of Medicine. National Academy of Sciences. Washington, DC.
- 106. CLAYSON, D. B. 1979. Bladder cancer in rats and mice: Possibility of artifacts. In Aspects of Cancer Research, 1971-1978, Editorials from the Journal of the National Cancer Institute. Natl. Cancer Inst. Monogr. 52: 519-525.
- 107. Peto, R. 1977. Epidemiology, multistage models, and short-term mutagenicity tests. In Origins of Human Cancer. H. H. Hiatt, J. D. Watson & J. A. Winsten, Eds.: 1403-1428. Cold Spring Harbor Laboratory. Cold Spring Harbor, NY.
- 108. GAYLOR, D. W. & R. L. KODELL. 1980. Linear interpolation algorithm for low-dose risk assessment of toxic substances. J. Environ. Pathol. Toxicol. 4: 305-312.
- 109. CRUMP, K. S. 1981. An improved procedure for low-dose carcinogenic risk assessment from animal data. J. Environ. Pathol. Toxicol. 5: 675-684.

REVIEW

Perspectives on Comparing Risks of Environmental Carcinogens'

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In 1987, investigators (Ames et al.) concluded that the risks of man-made industrial carcinogens and pesticides (outside of the workplace) are trivial compared with the risks of naturally occurring carcinogens found mostly in the diet. They used a ranking system based on human exposure and rodent potency (HERP) data to arrive at this conclusion. As a result, they recommend that regulatory agencies, such as the Environmental Protection Agency and the Food and Drug Administration, base their priorities in this area on their HERP system. We analyzed the assumptions and data set upon which the HERPs were based, concluding that such a simplified approach to set public health policy is inappropriate given the underlying uncertainties. However, we ote that when comparisons are consistently based on estinates of average daily exposure to common carcinogens, the HERP scores of many man-made pollutants are comparable to those of naturally occurring carcinogens in the diet. [J Natl Cancer Inst 1988;80:1282-1293]

Background

The majority (an estimated 60%-90%) of human cancer is considered to be attributable to environmental factors, broadly defined to include cigarette smoking, industrial pollutants, radiation, diet, and perhaps other life-style factors and viruses (1). Thus, in theory most cancer is preventable through the identification and control of causative factors, including exposure to carcinogens. For decades, policymakers, concerned with the assessment and regulation of environmental carcinogens have searched for a systematic way to set priorities among the many candidates. This paper critically evaluates the most recent proposal for such a ranking

Identification of specific etiologic factors and estimation of their relative importance constitute a formidable task. Few cancers are attributable to single factors or exposures; rather, complex interactions between environmental and host fac-

tors are generally involved (3-5). Moreover, because of the limitations of epidemiology (6), only rarely are human data available that directly link an environmental agent to human cancer. For example, epidemiological studies strongly suggest, although they do not conclusively establish, an association between organic chemical carcinogens in drinking water (such as chloroform) and cancers at several sites, including the rectum, colon, and bladder (7-11). Certain dietary and nutritional factors (such as dietary fat and fiber) have been implicated in cancer of the breast, colon, rectum, and stomach (12,13), but here too a direct causal association has not been established for specific dietary constituents. In addition to active cigarette smoking and a significant number of pollutants in the workplace, established to lung carcinogens (14), there is growing evidence sive smoking (15) and pollutants in the ambient air (16,17)contribute significantly to lung cancer mortality. However, because of cost and feasibility constraints and the difficulty in identifying an appropriate study population, the vast majority of animal carcinogens, both naturally occurring and man-made, have neither been the subject of epidemiological investigation nor are they likely to be (18). Thus, for practical purposes, as a matter of long-standing policy, regulatory agencies accept the use of positive animal data as predictive of carcinogenic hazard in human beings (19). The alternative, awaiting positive evidence of carcinogenicity in humans.

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traditionally has been rejected as morally and socially unacceptable.

A major limitation of epidemiology (and risk assessment) is that reliable data on human exposure to specific chemicals are frequently lacking. Therefore, by necessity, most epidemiological studies have relied on crude or indirect measures of exposure. A significant number of carcinogens have been detected in drinking water, ambient air, and the food supply; however, reliable monitoring data exist for only a small fraction of these chemicals. For example, while dozens of pesticides and industrial chemical carcinogens have been measured routinely in surface water, groundwater, and drinking water, they represent only a small percentage of chemical pollutants present (10,20-23). Over 700 organic chemicals have been found to be present in the U.S. drinking water supply, including 40 known or suspected carcinogens (24). Numerous carcinogenic air pollutants (trace metals, polycyclic aromatic hydrocarbons, and volatile organic chemicals) have been detected in ambient air, again, there are little or no reliable monitoring data on the majority of airborne carcinogens (25). Similarly, many carcinogenic pesticide residues have been identified in the food supply, but reliable exposure data are lacking for most (26). Testifying to the pervasiveness of environmental contamination are studies showing significant concentrations of synthetic organic chemicals in the blood, urine, and/or adipose tissue of the U.S. population. These include 1,1,1-trichloro-2,2-bis(p-chlorophenyl)ethane (DDT), dieldrin, heptachlor epoxide, polychlorinated biphenyls (PCBs), and dioxin (27,28). Again, data are far from comprehensive; however, they do show a decline in the concentrations of DDT and PCBs as a result of regulation.

Despite their limitations, available exposure and epidemiologic data have served as the basis for a number of widely varying estimates of the proportion of human cancer in the U.S. population that can be attributed to life-style, occupational exposures, or other environmental pollution. These exercises have generated significant debate, as much over the underlying assumptions as the data used to generate them (17,29-35). Unfortunately, various such estimates (ranging, for example, from 4% to >20% for occupational exposures) have been cited as a basis for setting priorities for public health protection. This approach ignores both the underlying uncertainties, the relative preventability of various risk factors (36), and the disproportionate impact on some segments of the population. For example, once recognized, most chemical pollutant hazards can be reduced or eliminated by practical means. Moreover, the involuntary nature of these exposures necessitates control at the source. in contrast to exposures related to life-style (e.g., diet and smoking), which can be addressed more effectively through public education regarding personal behavioral choices. Another inherent problem with the approach of estimates is that it obscures the much higher risks to certain subpopulations. For example, if the contribution of occupational carcinogens to all cancer deaths in the United States were as low as 3%, for male industrial workers as a group, workplace carcinogens would account for at least 25% of all identified causes of cancer (33).

Another tool that has been used increasingly by regulatory agencies to set priorities and even to determine acceptable levels of exposure to individual environmental contaminants has been quantitative risk assessment. Here, also, the lack of good information on human exposure as well as the usual paucity of epidemiological data are compounded by uncertainties regarding the proper way to extrapolate from high to low dose and from experimental animals to humans (37). To offset these uncertainties, the four major U.S. regulatory agencies, including the Environmental Protection Agency (EPA), the Occupational Safety and Health Administration (OSHA), the Consumer Product Safety Commission, and the Food and Drug Administration (FDA), have traditionally preferred conservative models that incorporate an assumption of low-dose linearity, regardless of the presumed mechanism of action of the chemical carcinogen (19). However, in certain instances, these conservative models may underestimate cancer risk. For example, the widely accepted linearized multistage model (38), considered to be one of the most conservative of the biologically plausible risk-assessment models, works on the assumption that the exposed population is of uniform susceptibility and that interactions do not occur between chemical exposures and other risk factors. Yet significant intraindividual variability has been demonstrated for human metabolism and binding of drugs and carcinogens (39-45) as well as for repair of DNA damage (46). Moreover, a number of epidemiological studies have demonstrated synergism between chemical exposures and host factors, such as cigarette smoking and air pollutants in the workplace and urban air (47,48). To further complicate the situation, although nonlinear (both superlinear and sublinear) dose-response relationships have been observed experimentally and epidemiologically, the available data do not allow low-dose linearity to be ruled out in any of these cases (49). Given these uncertainties, it is reassuring that, in a number of cases, risks observed in humans have been consistent with those calculated from high-dose animal experiments with the use of models that incorporated linearity at low dose. These include benzene, ethylene dibromide (EDB), gasoline, asbestos, and ethylene oxide (50-56). Therefore, there is general agreement that the use of quantitative risk assessment, performed with appropriate and consistent assumptions and models, affords the possibility of comparing risks for the purpose of setting priorities among selected candidates for regulation. However, most scientists do not view quantitative risk assessment as capable of providing precise estimates of human risk from individual chemicals: general sources of chemical exposures are considered even less likely candidates for risk estimation by this method.

Human Exposure/Rodent Potency (HERP) Index

Most recently, researchers at the University of California at Berkeley and Lawrence Berkeley Laboratory have suggested still another approach to priority setting (2). They have calculated a possible hazard index for selected carcinogens by expressing the human exposure (in milligrams/kilogram) as a percentage of the rodent TD₅₀ dose

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(also in milligrams/kilogram).⁴ They have compared the resultant HERP indices for four pollutants found in drinking water and indoor air, three man-made pesticides and other residues, 10 natural pesticides and dietary toxins, two food additives, five drugs, and two occupational exposures (see rable 1). The authors conclude that man-made environmen-

I pollutants, such as pesticide residues and contaminants in drinking water, are "likely to be of minimal carcinogenic hazard" relative to the background of natural carcinogens (found largely in the diet). They recommend that regulatory agencies that traditionally have emphasized control of exposures to man-made or industrial carcinogens (in addition to those in the occupational setting) revise their priorities.

The authors acknowledge several major limitations of the HERP system, such as the possibility of interspecies (rodent and human) variation in susceptibility to carcinogens and quantitative uncertainties regarding the general shape of the dose-response curve, including the possibility of synergistic effects and thresholds for nongenotoxic carcinogens, such as promoters (see discussion below). They caution that it would be a mistake to use the HERP index as a direct estimate of human hazard, but they conclude that the scale provides "a way of setting priorities for concern."

Although this is an innovative approach, it suffers from several inherent flaws. First, as we will show in table 2, the results are influenced strongly by the selection of chemicals and whether one classifies them as "man-made" or "natural." The rationale for selection of the individual compounds in table 1 was not provided by the authors, but presumably it was dictated by the nature and availability of both exposure and rodent potency data. As mentioned, the rodent potency data base is not comprehensive. For example, it omits a number of carcinogenic pesticides including alachlor, which is of current concern as a food contaminant (26) and has been found in water supply wells at significant concentrations (61). Certainly, the four selected drinking water and air

Here the TD to is the average daily dose rate to halve the percent of tumor-free animals by the end of a standard lifetime (57). The average TD₅₀ is calculated by taking the harmonic mean of the TD₅₀s of the positive tests in the most sensitive species. From each test, the target site with the lowest TD50 value was used. In general, the harmonic mean and the lowest TD₅₀ differ by a factor of =2 (58). The source of TD₅₀ values is the Carcinogenic Potency Data Base (CPDB) (57-60). The data base is a compilation of results from >3,500 experiments on 975 chemicals. It includes results from the Carcinogenesis Bioassay Program of the National Cancér Institute/National Toxicology Program (through May of 1986) as well as studies published in the literature (through December of 1984). The data base is restricted to tests that meet very stringent methodologic criteria. Thus certain human carcinogens (such as asbestos and tobacco smoke) are excluded; seven chemicals regarded by the International Agency for Research on Cancer (IARC) as having sufficient evidence of carcinogenicity in animals (cadmium chloride, cadmium sulfate, epichlorohydrin, glycidaldehyde, isosafrole, mestranole, and 2-nitropropane) are recorded in the CPDB as having only negative tests. The CPDB is a useful tool, but its limitations should be kept in mind.

Table 1. Possible carcinogenic hazards, as ranked by Ames et al. (2)*

| Possible hazard HERP %) | Carcinogenic exposure |
|---|---|
| | Man-made chemicals in foods and beverages |
| 0.0002 0.0003 0.0004 0.0002 | PCBs.† U.S. average daily dietary intake DDE/DDT.† average daily dietary intake EDB, average daily dietary intake from grains/grain products Furylfuramide in 2-fluorenamine, daily dietary intake before banning Saccharin† in 12-oz diet cola |
| 0.00 | Natural carcinogens in foods and beverages |
| 0.003 0.006 0.003 0.03 0.03 0.06 0.07 0.1 0.1 0.2 0.008 2.8 4.7 6.2 1.3 | DMN in 100 g of cooked bacon DEN in 100 g of cooked bacon Urethane in 250 mL of sake Symphytine in 1 cup of comfrey herb tea Aflatoxin in 1 peanut butter sandwich DEN in dried squid, broiled in gas oven Allyl isothiocyanate in 5 g of brown mustard Estragole in 1 g of dried basil leaf Hydrazines in 1 raw mushroom Safrole in natural root beer, before ban DMN in 12-oz beer, before 1979 Ethyl alcohol† in 12-oz beer Ethyl alcohol† in 250 mL of wine Comfrey root in comfrey-pepsin tablets, 9 daily Symphytine in comfrey-pepsin tablets, 9 daily |
| | Indoor air pollutants |
| 0.6 0.004 2.1 | Formaldehyde in conventional home air, 14 hr/day Benzene in conventional home air, 14 hr/day Formaldehyde in mobile home air, 14 hr/day |
| | Water pollutants |
| 0.001 0.004 0.0002 0.0003 0.008 | Chloroform† in tap water, 1 L U.S. average Tetrachloroethylene† in well water, 1 L, highly contaminated Chloroform† in well water, 1 L, contaminated Tetrachloroethylene† in well water, 1 L, contaminated Chloroform† in average swimming pool, 1 hr |
| | Drugs |
| 0.3 5.6 14 16 17 | Phenacetin, average dose Metronidazole, therapeutic dose Isoniazid, prophylactic dose Phenobarbital, 1 sleeping pill Clofibrate,† average daily dose |
| | Occupational exposure |
| 5.8 140 | Formaldehyde, worker's average daily exposure EDB, worker's daily intake, high exposure |
| *DMN = | = N-nitrosodimethylamine, and DEN $= N$ -nitrosodiethylamine. |

*DMN = N-nitrosodimethylamine, and DEN = N-nitrosodiethylamine.

pollutants and the pesticides listed cannot represent the large number of industrial chemicals and pesticides that have been detected frequently in the U.S. drinking water, air, and food supply and that also have evidence of carcinogenicity in humans and/or laboratory animals (62,63).

Moreover, although we are aware that there are many potential dietary hazards, the majority of which also are not well characterized (2,64), the 10 natural dietary carcinogens in table 1 include a number of exotic foods to which the U.S. general population has limited exposure (sake, comfrey

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[†] Carcinogens characterized by Ames et al. as nongenotoxic and likely to have thresholds.

herb tea, dried squid, brown mustard, and comfrey-pepsin tablets). Therefore, comparisons between drinking 1 L of water containing average concentrations of chloroform and eating a daily serving of dried squid ignore the fact that the average American adult ingests an estimated 2 L or more of water a day (65)⁵ and rarely, if ever, eats dried squid.

An additional problem is that several "natural pesticides and dietary toxins" in table 1 are misclassified in that they can result from harvesting, manufacturing, or cooking processes and therefore cannot be considered to be strictly natural. For example, aflatoxin in nuts and grains is partially attributable to improper harvesting and storage procedures, whereas, as the authors acknowledge, nitrosamines are formed in cured meats through the reaction of secondary amines with nitrites added as preservatives. Carcinogenic nitropyrenes and nitrosamines occur in browned or burned meats as a result of cooking with gas flames that generate NO_2 (2).

Moreover, a number of natural substances or food additives in table 1 have been banned (safrole in natural root beer and AF-2, a Japanese food additive never used in the United States) (67), so that there is no current exposure to the U.S. population. Several of the environmental pollutants have been regulated (chloroform, PCBs, and EDB) or even banned (DDT), so that postregulatory exposures (and HERPs) are predictably low, testifying to the effectiveness of regulation.

A second major limitation of the approach of Ames et al. derives from the fact that, as can be seen in table 1, varying exposure indices were used. For waterborne and airborne contaminants, daily exposure was calculated; for pesticides and other residues in food, daily average dietary intake was provided; for "natural" carcinogens in food, one serving was assumed to occur daily; for food additives and drugs, several different measures were used.

To illustrate the effect of chemical selection and of assumptions regarding levels of exposure, we have constructed table 2; it includes all of the chemicals/exposures in table 1, except for those dietary constituents not widely consumed in the United States and those that have been banned and have no current U.S. exposure. We have also omitted drugs because exposure is generally of short duration; drugs are a special case because they are prescribed when benefits are thought to outweigh risks to the individual. Finally, we have included in table 2 several chemicals or sources of exposure that are encountered commonly by the U.S. population and for which rodent potency (58-60) and exposure data are available. Unfortunately, in several cases environmental chemicals of concern were in the rodent potency data base, but we could not find reliable exposure data for specific media. This was true for dioxin or 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD). However, according to the EPA, a crude estimate of total daily intake of

To avoid the problems of inconsistent exposure indices, we have adopted in table 2 the standard approach of uniformly providing average daily dose to the U.S. adult. We recognize both the uncertainties in available exposure data (143) and the fact that the average estimates mask wide interindividua. variation in exposure depending on geographical, cultural, economic, social, and host factors. For example, a child's exposure to pollutants in drinking water is proportionally greater than exposure of the adult, because children ingest an estimated 1 L of water per 10 kg of body weight compared with 2 L or more per 70 kg of body weight for the adult (65). Children may also consume more of a contaminated food than adults. In the case of the pesticide daminozide, the daily dose to the U.S. child (1-6 yr) from consumption of apples, apple juice, and peanut butter is from fivefold to 15-fold higher than the daily dose to the U.S. adult (70.71.)

Thus, there are obvious drawbacks to using each of the possible exposure indices (average, worst case, general population, or sensitive subpopulation). However, it is imperative in making comparisons that the same measure of exposure be used consistently. This is demonstrated by table 3 in which we compared HERPs from tables 1 and 2 for the same compound.

As mentioned above, postregulatory exposures (and HERPs) for environmental carcinogens such as DDT/DDE (1,1-dichloro-2,2'-bis(p-chlorophenyl)ethylene) are low. Therefore, in a number of cases we have included preregulatory and postregulatory values for purposes of comparison.

Unfortunately, any listing of chemicals such as in tables 1-3 cannot convey the reality of cumulative exposures to different carcinogens in the same medium. Also, it does not reflect the possibility of interactions among them or the need to consider exposures to the same chemical via several different media. For example, the individual has exposure to synthetic volatile organic compounds in the drinking water from ingestion, from dermal absorption while bathing or showering, and from inhalation of the volatilized compound (144). Humans may be exposed concurrently to the same carcinogenic substance via a number of different sources and media. For example, in considering the risk of EDB in grain, the New York Department of Health reasonably chose to sum the potential risks of the pesticide in food, ambient air (from use of unleaded gas), and drinking water (145).

Finally, an important distinction not conveyed by either table 1 or table 2 is that between voluntary and involuntary exposure. As discussed in the introduction, individuals are capable of voluntarily reducing exposure to substances in diet and cigarette smoke that have been identified as carcinogenic hazards. By contrast, individuals cannot feasibly control their exposure to air, water, and workplace pollution.

In tables 2 and 3, we have attempted to demonstrate the susceptibility of the HERP system (or any such simplified approach) to the effects of selection of both chemicals and exposure estimates. As is clear from table 3, the differences between tables 1 and 2 are largely because of these two factors. In contrast to that of Ames et al. (2), our approach, incorporating a representative set of exposures to the U.S.

dioxin by sizeable segments of industrialized populations is 1 pg/kg (28), which corresponds to a HERP of 0.004.

To avoid the problems of inconsistent exposure indices we

In fact, the results of a recent water consumption survey show that for 5% of adults 20-64 yr old, the average daily consumption of tap water is 2.71 L/day, whereas the average daily total water intake is 3.79 L (66).

Table 2. Ranking possible carcinogenic hazards with the use of the methodology of Ames et al. (2)*

| Possible hazard HERP %) | Carcinogenic exposure | Average daily carcinogen dose (70-kg adult) | Potency of carcinogen TD 50 (mg/kg) | Comment |
|-------------------------------|--|---|-------------------------------------|--------------|
| | Man-made chemicals in | foodsibeverages | | |
| | | | | |
| 0.02 | Daminozide in treated apples and apple juice (1987) | 20 μg | 1.2 | (1) |
| 0.002 | Daminozide in peanuts and peanut butter (1987) | 1.9 μg | £ 1.2 0.24 | (1) |
| 0.03 | DBCP in treated carrots (preregulatory, 1976) | 5.1 µg | . 0.24 | (2) |
| 0.003 | DDT, DDD, and DDE in food (preregulatory, | 29.0 µg | 13 | (3) |
| 0.0003 | 1968-1969) DDT, DDD, and DDE in food (postregulatory, (1980-1982) | 2.3 μg | 13 | (3) |
| 0.002 | Dieldrin in food (preregulatory, 1968-1969) | 1.5 µg | 1.1 | (4) |
| 0.001 | Dieldrin in food (postregulatory, 1980–1982) | 1.1 μg | 1.1 | (4) |
| 0.004 | EI)B in treated apples (preregulatory) | 4.1 µg | 1.5 | (5) |
| 0.0004 | EI)B in grain products (preregulatory, 1983) | 0.42 µg | i.5 | (5) |
| 0.01 | PCBs in food (preregulatory, 1971) | 15 μg | 1.7 | (6) |
| 0.0002 | PCBs in food (postregulatory, 1980-1982) | 0.2 µg | 1.7 | (6) |
| 0.003 | Sodium saccharin in diet soda (1977-1978) | 4.9 ng | 2.100 | (7) |
| 0.003 | Natural carcinogens in foo | • | 2,100 | (,, |
| 0.003 | · | • | . 0.0026 | / 0 \ |
| 0.003 | Aflatoxins in peanuts and peanut butter (1977) | 5.8 ng | · 0.0026 52 | (8) |
| (0.0001 | Estragole in basil | <3.8 μg | | (9) |
| 1.6 | Ethyl alcohol in beer (1981) | 10.2 g | 9.100 | (10) |
| 0.4 | Ethyl alcohol in wine (1981) | 2.7 g | 9.100 | (10) |
| 1.3 | Ethyl alcohol in hard liquor (1981) | 8.1 g | 9.100 | (10) |
| 0.01 | Hydrazines in mushrooms (1977) | 0.16 g | 20,000 | (11) |
| 0.001 | DMN in cured meat and bacon (1980) | 0.12 μg | 0.16 | (12) |
| 0.002 | DEN in cured meat and bacon (1980) | 0.034 μg | 0.021 | (12) |
| | Ambient air pol | | | |
| 0.03 | Benzene (Los Angeles, preregulatory, 1968) | · 1.0 mg | 53 | (13) |
| 0.009 | Benzene (Los Angeles, postregulatory, 1984) | 0.32 mg | 53 | (13) |
| 0.0005 | Carbon tetrachloride (U.S. urban and surburban areas, 1973-1974) | 48 µg | 140 | (14) |
| 0.0004 | Carbon tetrachloride (U.S. urban areas, 1980) | 42 μg | 140 | (14) |
| 0.0002 | DDT (U.S. rural areas, preregulatory, 1972) | 2.0 µg | 13 | (15) |
| 0.00003 | DDT (U.S. rural areas, postregulatory, 1974) | 0.24 µg | 13 | (15) |
| 0.004 | EDB (U.S. urban areas, 1980-1981) | 4.3 µg | 1.5 | (16) |
| 1.8 | Formaldehyde (Los Angeles, 1966) | 1.9 mg | 1.5 | (17) |
| 0.4 | Formaldehyde (Los Angeles, 1979) | 370 μg | 1.5 | (17) |
| 0.002 | PCBs (U.S. suburban areas, preregulatory, 1975) | 2 μg | 1.7 | (18) |
| 0.0001 | PCBs (U.S. urban areas, postregulatory, 1979) | 150 ng | 1.7 | (18) |
| 0.003 | Tetrachloroethylene (Bayonne, NJ, 1973) | 220 µg | 100 | (19) |
| 0.001 | Tetrachloroethylene (Bayonne, NJ, 1983) | 92 µg | 100 | (19) |
| 0.001 | Toxaphene (U.S. rural areas, 1972) | 5.2 μg | 5.8 | (20) |
| | Indoor air poll | | | |
| 0.005 | Benzene (personal average, New Jersey, 1981) | 173 µg | 53 | (21) |
| 0.0002 | Carbon tetrachloride (personal average, New Jersey, 1981) | 16.2 μg | 140 | (22) |
| 0.01 | Chlordane (average in treated homes, 1976-1982) | 20.5 μg | 2.4 | (23) |
| 0.6 | Formaldehyde in conventional homes (average of all reported U.S. data) | 600 µg | 1.5 | (24) |
| 2.1 | Formaldehyde in mobile homes (U.S. average, 1984) | 2.2 mg | 1.5 | (24) |
| 0.02 | Heptachlor (average in treated homes, 1982) | 13.9 µg | 1.2 | (25) |
| 0.001 | Tetrachloroethylene (personal average, New Jersey, | 80 μg | 100 | (26) |
| | 1981) | | | ., |
| | Water pollut | anis | | |
| 1000.0 | Chlordane (Kansas City drinking water, preregulatory, 1965-1967) | 0.14 µg | 2.4 | (27) |
| 0.003 | Chloroform (average U.S. drinking water, 1976) | 170 µg | 90 | (28) |
| 0.01 | DBCP (California, postregulatory, 1984) | 2.0 µg | 0.24 | (29) |
| 0.007 | EDB (Florida, groundwater, 1983) | 7.8 µg | 1.5 | (30) |
| 0.03 | Heptachlor (South Carolina rural drinking water, | 24 μg | 1.2 | (31) |
| | preregulatory, 1977) | , 5 | | |
| 0.0003 | FCBs (U.S. surface water, preregulatory, | 0.4 µg | 1.7 | , (32) |
| 0.0002 | 1971–1974) Tetrachloroethylene (New Jersey water supplies, | 12 µg | 100 | (33) |
| ~.~~~ | | | | |
| | 1985) | | | |
| 0.00002 | 1985) TCE (U.S. water supplies, 1985) Vinylidine chloride (New Jersey water supplies, | 14 дв | 940 24 | (34) (35) |

Table 2. Continued

| Possible hazard c (HERP %) | Carcinogenic exposure | Average daily carcinogen dose (70-kg adult) | Potency of carcinogen TD ₅₀ (mg/kg) | Comment† |
|--|--|---|--|--|
| | Occupational ex | posures | | |
| 32.3 0.06 105.0 3.0 6.2 0.2 | Benzene (rubber industry, preregulatory, 1942) Benzene (rubber industry, postregulatory, 1980s) Formaldehyde (resin and paper manufacture, 1961) Formaldehyde (resin and plastic manufacture, 1980s) TCE (small factories, preregulatory, 1940s) TCE (postregulatory, 1980s) | 1.2 g 2.4 mg 110 mg 3.2 mg 4.1 g 0.1 g | 53 53 1.5 1.5 940 940 | (36) (36) (37) (37) (38) (38) |

^{*}The selection of chemicals and the estimates of exposure differ somewhat from those in Ames et al., as described in the text. To calculate average daily dose over an individual lifetime, we assumed: a) food consumption according to nationwide surveys; b) water consumption: 2 L/day; c) ambient air. inhalation of 20,000 L/day; d) indoor air. inhalation of 10,800 L/14-hr day; e) workplace air. inhalation of 9,600 L/day, 5 days/wk, 50 wk/yr, 40/70 yr (i.e., 3,768 L/day over an average lifetime) (68). For carcinogens listed as ambient and indoor air pollutants, the respective HERPs cannot be considered additive, since the 20,000 L/day may include both types of exposure. We also calculated exposure for a 70-kg male adult, although a 60-kg adult is more reasonable (69). When only a range of values was reported in the literature, their geometric mean was used as the average exposure. The HERP is derived by dividing the daily carcinogen dose by 70 kg to provide a milligram-per-kilogram value, which is then given as the percentage of the TD₅₀ dose in the rodent (also in mg/kg).

†See appendix for comments.

Table 3. Comparison of possible carcinogenic hazards (HERPs) as estimated by Ames et al. and with the use of average exposure estimates 2.1

| Carrierante | Ames et | Our estimate. | | | | | |
|--|------------------|---------------------|---------------------|--|--|--|--|
| Carcinogenic exposure | Average exposure | Worst-case exposure | average exposure | | | | |
| Man-made chem | icals in food | s and beverage | \$ | | | | |
| DDE/DDT in food | | | | | | | |
| Preregulatory | | _ | 0.003 | | | | |
| Postregulatory | 0.0003 | _ ` | 0.0002 | | | | |
| EDB in grains | 0.0004 | | 0.0004 | | | | |
| PCBs in food | | | | | | | |
| Preregulatory | - | _ | 0.01 | | | | |
| Postregulatory | 0.0002 | _ | 0.0002 | | | | |
| Sodium saccharin in diet sodas | _ | 0.06 | 0.003 | | | | |
| Natural carcinogens in foods and beverages | | | | | | | |
| Aflatoxins in peanuts and peanut butter | _ | 0.03 | 0.003 | | | | |
| DMN in cured meat and bacon | | 0.003 | 0.001 | | | | |
| DEN in cured meat and bacon | _ | 0.006 | 0.002 | | | | |
| Estragole in basil | _ | 1.0 | < 0.0001 | | | | |
| Ethyl alcohol in beer | — | 2.8 | 1.6 | | | | |
| Ethyl alcohol in wine | _ | 4.7 | 0.4 | | | | |
| Hydrazines in mushrooms | _ | 0.1 | 0.01 | | | | |
| Ambie | nt air pollut | ants | | | | | |
| Formaldehyde in conventional home air | 0.6 | _ | 0.6 | | | | |
| Formaldehyde in mobile home air | 2.1 | | 2.1 | | | | |
| Water pollutants | | | | | | | |
| Chloroform in water | 0.001 | _ | 0.003 | | | | |
| Tetrachloroethylene in water | - | 0.0003 | 0.0002‡ | | | | |
| TCE in water | | 0.004 | 0.000025 | | | | |
| Occupational exposures | | | | | | | |
| Formaldehyde in workplace air | 5.8 | - | 3.0 | | | | |

^{*}DMN = N-nitrosodimethylamine, DEN = N-nitrosodiethylamine, and TCE = trichloroethylene.

population, shows that the selected man-made or industrial pollutants generally are comparable in terms of HERP scale to naturally occurring carcinogens in the diet. Because of the limitations in the HERP approach, however, we stress that regulatory agencies would be unwise to base public health policies principally on comparisons such as these.

Finally, Ames et al. (2) asserted that nine of the 26 carcinogens listed in table 1 "are thought to be nongenotoxic" and are therefore likely to have nonlinear dose-response curves or a decreased risk at lower dose. This subject has been discussed frequently (146-149). The general consensus on the part of regulatory agencies and expert groups has been that such policy distinctions are premature because they are supported inadequately by scientific data (19,63,147,150,151).

There are few, if any, clear-cut promoters and initiators; rather, there is evidence that under different conditions the same carcinogen can operate as a complete carcinogen, an initiator, or a promoter (147). For example, TCDD has demonstrated the ability to act both as a complete carcinogen and a promoter (152-155). It is just as difficult to distinguish between genotoxic and nongenotoxic agents because in most cases short-term tests for genetic toxicity have generated a mixture of positive and negative results. This phenomenon has been observed with a variety of chemicals regarded up to this time as model "epigenetic, late stage" carcinogens: asbestos, the phorbol ester 12-O-tetradecanoylphorbol-13-acetate, diethylstilbestrol, and DDT. These compounds have induced a variety of genetic effects, either indirectly or directly, in experimental systems or in humans (149).

The nine so-called nongenotoxic carcinogens in table 1 illustrate the difficulty of making such categorical distinctions. Although in most instances the majority of short-term test results have been negative, each of the compounds (with the exception of clofibrate) has tested positive in at least one assay for each of several different genetic toxicity end points

[†] See tables 1 and 2 for details on daily carcinogenic dose and TD50.

[#]Worst-case assumption: HERP % = 0.007.

[§] Worst-case assumption: HERP % = 0.1.

cence of genetic toxic effects is generally limited, it cannot be dismissed. Therefore, it is not possible to conclude definitively that these are nongenotoxic carcinogens that do not act at some stage and under some conditions, either directly or indirectly, by damaging the genetic material. Viewed in a larger context, the proposed distinction among carcinogens on the basis of presumed mechanism or stage at which they act is belied by the observation that control of late-stage carcinogens that may not be genotoxic may lead to the most rapid reduction in risk, as has been seen with postmenopausal estrogen therapy and cigarette smoking (158).

In summary, there is no question that both occupational and food carcinogens are real concerns. However, while the hazards of the workplace are relatively well characterized (68), there is clearly a need for more research on dietary carcinogens. At the same time, there is evidence from epidemiologic, experimental, and monitoring sources that the cumulative risks of environmental pollution are important. Despite its limitations, the HERP analysis for a selection of exposures prevalent in the U.S. environment tends to support this conclusion. Although it is not possible to estimate the magnitude of these risks with certainty, it is prudent to con-

⁶As summarized by the IARC, chloroform has been positive in only one of many assays for gene mutation in bacteria and has been largely negative in other systems used. However, it has tested positive in lower eukaryotic systems (inducing differential toxic effects in DNA repair-deficient strains, gene conversion, and/or recombination and reverse mutation). Trichloroethylene has been positive in a number of assays. It has induced genetic toxic effects in bacteria (mutation), in yeast (gene conversion or recombination and mutation), in Tradescuntia (mutation), in rodent cells (transformation), in human cells in vitro (unscheduled DNA synthesis (UDS) and sister chromatid exchanges (SCEs)], in animals in vitro (DNA damage), and in animal cells in vivo (mutation and micronuclei). Tetrachloroethylene, PCBs, and DDT have been largely negative in assays for genetic toxic effects; however, for tetrachloroethylene there have been positive results in yeast (recombination or gene conversion), in Tradescantia (mutation), and in animal cells (transformation and DNA damage). PCBs have induced DNA damage in animal cells in vitro and UDS in rat primary hepatocytes. DDT has been positive in insect systems (dominant lethal mutation and aneuploidy), animal cells in vitro (chromosome aberrations), and animal cells in vivo (chromosome aberrations and dominant lethal mutation). Ethyl alcohol has been studied extensively; a significant number of positive results were found. Evidence of genetic toxic effects includes gene conversion or recombination, mutation, and aneuploidy in lower eukaryotic systems; SCE, micronuclei, and chromosome aberrations in plant systems; SCE, chromosome aberrations, and aneuploidy in animal cells in vitro; SCE, chromosome aberrations, micronuclei, dominant lethal mutations, and aneuploidy in animal cells in vivo: and SCE and chromosome aberrations in human cells in vivo. Alcoholism, is associated with increased incidence of chromosome aberrations (157). For phenobarbitol, the preponderance of results has been negative. However, there is evidence for the induction of gene mutation in bacteria and aneuploidy in yeast gene mutation, SCE, and chromosome aberrations in rodent cells in vitro; cell transformation in rodent cells; as well as gene mutation and chromosome aberrations in human cells in vitro. Clofibrate has only been tested in two assays, both of which were negative. Finally, sodium saccharin has evidence of genetic toxic effects in lower eukaryotic systems (gene conversion or recombination and mutation), in insects (mutation), in animal and human cells in vitro (SCE and chromosome aberrations), and in animals in vivo (SCE and mutation).

tinue to reduce involuntary exposures to caremogens. The dramatic decrease in estimated cancer risk following regulation of a number of industrial chemicals illustrates this point. Controlling exposures to carcinogens such as those listed in table 2 has important side benefits in that many carcinogens are mutagenic, teratogenic, reproductive, or neurological toxicants (36).

References

- HIGGINSON J, MUIR CS. The role of epidemiology in elucidating the importance of environmental factors in human cancer. Cancer Detect Prev 1976:1:79-105.
- AMES BN, MAGAW R, GOLD LS. Ranking possible carcinogenic hazards. Science 1987:236:271-280.
- HIATT HH, WATSON JD, WINSTEN JA, eds. Origins of human cancer. Cold Spring Harbor, NY: Cold Spring Harbor Laboratory, 1977.
- MULVIHILL IJ. Genetic repertory of human neoplasia. In: Mulvihill, IJ, Miller RW, Fraumeni JF Jr. eds. Genetics of human cancer. New York: Raven Press, 1977:137-143.
- MILLER DG. On the nature of susceptibility to cancer. Cancer 1980;46:1307-1318.
- DAY NE. Statistical considerations. In: Wald NJ, Doll R, eds. Interpretation of negative epidemiologic evidence of carcinogenicity. Lyon, France: IARC, 1985:13-27.
- WILKINS JR, REICHES NA, KRUSE CW. Organic chemical contaminants in drinking water and cancer. Am J Epidemiol 1979;110:420-448.
- National Research Council. Drinking water and health, vol 3. Washington, DC: Natl Acad Press, 1980.
- GÖTTLIEB MS, CARR JK, CLARKSON JR. Drinking water and cancer in Louisiana: a retrospective mortality study. Am J Epidemiol 1982;116:652-667.
- CRUMP KS, GUESS HA. Drinking water and cancer: review of recerepidemiological findings and assessment of risks. Annu Rev Public Health 1982;3:339-357.
- CANTOR KP, HOOVER R, HARTGE P, et al. Bladder cancer, drinking water source, and tap water consumption: a case-control study. JNCI 1987;79:1269-1279.
- MACLURE KM, MACMAHON B. An epidemiologic perspective of environmental carcinogenesis. Epidemiol Rev 1980;2:19-48.
- 13. Cohen L. Diet and cancer. Sci Am 1987;257:42-48.
- DECOUFLÉ P. Occupation. In: Schottenfeld D. Fraumeni JF Jr. eds. Cancer epidemiology and prevention. Philadelphia: Saunders. 1982;318-335.
- National Research Council. Environmental tobacco smoke: measuring exposures and assessing health effects. Washington, DC: Natl Acad Press, 1986.
- 16. BLOT WJ. Clues to environmental determinants of cancer from its geographic patterns: In: Breslow NE, Whittemore AS, eds. Energy and health. Proceedings of a SIMS conference. Philadelphia: SIAM, 1979:151-167.
- 17. NISSET ICT, SCHNEIDERMAN MA, KARCH NJ, et al. Review and evaluation of evidence for cancer associated with air pollution. Research Triangle Park: EPA Office of Air Quality Planning and Standards, 1984 (publication No. (EPA) 450/5-83-006R).
- KARSTADT M, BOBAL R, SELIKOFF IJ. A survey of availability of epidemiologic data on humans exposed to animal carcinogens. In: Peto R, Schneiderman M, eds. Quantification of occupational cancer. Banbury report No. 9. Cold Spring Harbor, NY: Cold Spring Harbor Laboratory, 1981:223-242.
- Office of Technology Assessment. Identifying and regulating carcinogens. Washington, DC: US Govt Print Off, 1987.
- Council on Environmental Quality. Contamination of groundwater by toxic organic chemicals. Washington, DC: US Govt Print Off, 1981.
- Office of Technology Assessment. Protecting the nation's groundwater from contamination. Washington, DC: US Govt Print Off, 1984 [publication No. (OTA)-0-233].
- National Research Council. Drinking water and health, vol 1-6. Washington, DC: Natl Acad Press, 1977-1987.
- WALLACE LA, PELLIZZARI ED, HARTWELL TD, et al. The TEAM study: personal exposures to toxic substances in air, drinking water, and breath of 400 residents of New Jersey, North Carolina and North Dakota. Environ Res 1987;43:290-307.
- HARRIS RH, PAGE T, REICHES NA. Carcinogenic hazards of organic chemicals in drinking water. In: Hiatt HH, Watson JD, Winsten JA.

- eds. Book A. Incidence of cancer in humans. Cold Spring Harbor, NY: Cold Spring Harbor Laboratory, 1977;309-330.
- 25. HUNT WF JR, FACRO RB, CURRAN TC, et al. Estimated cancer incidence rates for selected toxic air pollutants using ambient air pollution data. Research Triangle Park: EPA Office of Air and Radiation, 1984.
- 26. National Academy of Sciences. Regulating pesticides in food: the Delaney paradox. Washington, DC: Natl Acad Press, 1987.
 - 27. MURPHY RS, KUTZ FW, STRASSMAN SC. Selected pesticide residues or metabolites in blood and urine specimens from a general population survey. Environ Health Perspect 1983;48:81-86.
 - Environmental Protection Agency. A cancer risk-specific dose estimate for 2.3.7.8-TCDD (draft). Washington DC: EPA, 1987.
 - COLE P. Cancer and occupation: status and needs of epidemiologic research. Cancer 1977;39:1788-1791.
 - BRIDBORD K, DECOUFLÉ P, FRAUMENT JF JR, et al. Estimates of the fraction of cancer in the United States related to occupational factors. National Cancer Inst., NIEHS and NIOSH, September 15, 1978 (reproduced in ref. 18, pp. 701-726).
 - CEDERLOF R. DOLL R. FOWLER B. et al. Air pollution and cancer. risk assessment methodology and epidemiological evidence. Environ Health Perspect 1978;22:1-12.
 - DOLL R, PETO R, eds. The causes of cancer: quantitative estimates of avoidable risk of cancer in the United States today. London: Oxford Univ Press, 1981.
 - NICHOLSON WJ. Quantitative estimates of cancer in the workplace. Am J Ind Med 1984;5:341-342.
 - PIKE MC, GORDON RJ, HENDERSON BE, et al. Air pollution. In: Fraumeni JF Jr, ed. Persons at high risk of cancer. An approach to cancer etiology and control. New York: Academic Press, 1975:225-238.
 - DAVIS DL, LILIENFELD AD, GITTELSOHN A, et al. Increasing trends in some cancers in older Americans: fact or artifact. Toxicol ind Health 1986:2:127-144.
 - TOMATIS L. Relation between mutagenesis, carcinogenesis, and teratogenesis: experience from the IARC monographs programme. Presented at the fourth international conference on environmental mutagens, Stockholm, June 24-28, 1985.
 - PERERA F. Quantitative risk assessment and cost benefit analysis for carcinogens at EPA: a critique. J Public Health Policy 1987;8:202-221.
 - Environmental Protection Agency. Guidelines for carcinogen risk assessment. Federal Register, September 24, 1986;51:33992-34003.
 - CARTWRIGHT RA, ROGERS HJ, BARHAM-HALL D, et al. Role of N-acetyltransferase phenotypes in bladder carcinogenesis: a pharmacogenetic epidemiologic approach to bladder cancer. Lancet 1982;2:842-845.
 - HARRIS CC, TRUMP BF, GRAFSTROM R, et al. Differences in metabolism of chemical carcinogens in cultured human epithelial tissues and cells. J Cell Biochem 1982;18:285-294.
 - RITCHIE JC, IDLE JR. Population studies of polymorphism in drug oxidation and its relevance to carcinogenesis. In: Bartsch H, Armstrong, B. eds. Host factors in human carcinogenesis (IARC Sci Publ No. 39). Lyon. France: IARC, 1982;381-394.
 - OMENN GS. Advances in genetics and immunology: the importance of basic research to prevention of occupational diseases. Arch Environ Health 1984;39:173-182.
 - MARQUIS JK, SIEK GC. Sensitive populations and risk assessment in environmental policy-making. In: Saxena J, ed. Hazard assessment of chemicals, vol 6. Washington, DC: Hemisphere, 1988.
 - 44. PERERA F. The significance of DNA and protein adducts in human biomonitoring studies. Mutat Res 1988;205:255-269.
 - 45. HATTIS D, ERDREICH L, DIMAURO T, Human variability in parameters that are potentially related to susceptibility to carcinogenesis. I. Preliminary observations. Cambridge, MA: M.LT. Center for Technology, Policy and Industrial Development, 1986 (report No. CTPID 86-4).
 - SETLOW RB. Variations in DNA repair among humans. In: Harris CC. Autrup H. eds. Human carcinogenesis. New York: Academic Press, 1983:231-254.
 - SELIKOFF IJ. Lung cancer and mesothelioma during prospective surveillance of 1249 asbestos insulation workers, 1963-1974. Ann NY Acad Sci 1976;271:448-456.
 - ARCHER VE. Enhancement of lung cancer by cigarette smoking in uranium and other miners. Carcinog Compr Surv 1985;8:23-37.
 ZEISE L. WILSON R. CROUCH EAC. Dose-response relationships for
 - 49. ZEISE L. WILSON R. CROUCH EAC. Dose-response relationships for carcinogens: a review. Environ Health Perspect 1987;73:259-308.
 - 50. CROUCH E, WILSON R. Interspecies comparison of careinogenic potency. J Toxicol Environ Health 1979:5:1095-1118.
 - California Department of Health Services. Health effects of benzene, report to the scientific review panel, part B. Sacramento, CA: CDHS, 1984.

- Rowe JN, Springer JA. Asbestos lung cancer risks: comparison of animal and human extrapolation. Risk Anal 1986;6:171-180.
- 53. ENTERLINE PE. A method for estimating lifetime cancer risks from limited epidemiologic data. Risk Anal 1987;7:91-96.
- HERTZ-PICCIOTTO I. NEUTRA RR. COLLINS JF. Ethylene oxide and leukemia. JAMA 1987:257:2290.
- 55. HERTZ-PICCIOTTO, I. GRAVITZ N, NEUTRA RR. How do cancer risks predicted from animal bioassays compare with the epidemiologic evidence? The case of ethylene dibromide. Risk Anal. In press.
- 56. California Department of Health Services. Controlling risks from low dose exposure to proposition 65 carcinogens and reproductive toxins. DHS response to the proposed science advisory panel caveat. Sacramento, CA: CDHS. December 23, 1987.
- 57. Peto R, Pike MC, Bernstein L, et al. The TD₅₀ a proposed general convention for the numerical description of the carcinogenic potency of chemicals in chronic-exposure animal experiments. Environ Health Perspect 1984:58:1-8.
- 58. GOLD LS, SLONE TH, BACKMAN GM, et al. Second chronological supplement to the carcinogenic potency data base: standardized results of animal bioassays published through December 1984. Environ Health Perspect 1987;74:237-329.
- GOLD LS, SAWYER CB, MAGAW R, et al. A carcinogenic potency data base of the standardized results of animal bioassays. Environ Health Perspect 1984;58:9-13.
- GOLD LS, DE VECIANA M, BACKMAN GM, et al. Chronological supplement to the carcinogenic potency data base: standardized results of animal bioassays published through December 1982. Environ Health Perspect 1986;67:161-200.
- 61. HALLBERG GR, LIBRA RD, LONG KR, et al. Pesticides, groundwater and rural drinking water quality in Iowa. In: Pesticides and groundwater: a health concern for the Midwest. Navarre, MN: Public Freshwater Foundation, 1987:83-104.
- National Toxicology Program. Fourth annual report on carcinogens: summary 1985. Research Triangle Park, NC: NTP, 1985 [publication No. (NTP)85-002].
- 63. International Agency for Research on Cancer. Overall evaluations of carcinogenicity: an updating of IARC monographs, vol 1-42. IARC Monogr Eval Carcinog Risk Chem Hum (suppl 7). Lyon, France: IARC, 1988.
- SUGIMURA T, SATO S. Mutagens-carcinogens in foods. Cancer Res 1983;43(suppl):2415S-2421S.
- National Research Council. Drinking water and health, vol 6. Washington, DC: Natl Acad Press, 1986.
- ERSHOW AG, CANTOR KP. Population-based estimate of water intake. Fed Proc 1986;45:706.
- International Agency for Research on Cancer. Some food additives, feed additives, and naturally occurring substances. IARC Monogr Eval Carcinog Risk Chem Hum 1983;31:47-61.
- 68. GOLD LS, BACKMAN GM, HOOPER NK, et al. Ranking the potential carcinogenic hazards to workers from exposures to chemicals that are tumorigenic in rodents. Environ Health Perspect 1987;76:211-219.
- Environmental Protection Agency. Captan special review position document 2/3. Washington, DC: EPA, Office of Pesticides and Toxic Substances, 1985.
- Environmental Protection Agency. Daminozide special review. Phase III market basket survey, 1987 [Uniroyal's submissions dated February 13 and 20, 1987; and April 13, 1987 (memo from L. Cheng to W. Waldrop, May 18, 1987)].
- Environmental Protection Agency. Tolerance assessment system. Annualized chronic consumption data based upon the United States Department of Agriculture 1977 nationwide food consumption survey. Washington, DC: EPA, Office of Pesticide Programs, 1987.
- NEWSOME WH, IVERSON F, PANOPIO LG, et al. Residues of dibromochloropropane in root crops grown in furnigated soil. J Agr Food Chem 1977;25:684-685.
- DUGGAN RE, CORNELIUSSEN PE. Dietary intake of pesticide chemicals in the United States (III), June 1968-April 1970. Pest Mont J 1972;5:331-341.
- Environmental Protection Agency. DDT: a review of scientific and economic aspects of the decision to ban its use as a pesticide. Washington, DC: EPA, 1975 [publication No. (EPA) 540/1-75-022].
- GARTELL MJ. CRAUN JD. PODREBARAC DS, et al. Pesticides, selected elements and other chemicals in adult total diet samples, October 1980-March 1982. J Assoc Off Anal Chem 1986:69:146-161.
- DUMAS T. Inorganic and organic bromide residues in foodstuffs fumigated with methyl bromide and ethylene dibromide at low temperatures. J Agr Food Chem 1983;21:433-436.
- 77. Environmental Protection Agency. Ethylene dibromide (EDB). Scien-

- tific support and decision document for grain and-grain milling fumigation uses. Washington, DC: EPA, 1984.
- JELINEK CF, CHRNELIUSSEN PE. Levels of PCBs in the U.S. food supply. In: Proceedings of the national conference on polychlorinated biphenyls, Chicago, 1975. Washington, DC: EPA, 1976:163-165 [publication No. (EPA)560/6-75-004].
- International Agency for Research on Cancer. Some non-nutritive sweetening agents. IARC Monogr Eval Carcinog Risk Chem Hum 1980;22:111-170.
- PAO EM. FLEMING KH. GUENTHER PM. Foods commonly eaten by individuals: amount per day and per eating occasion. Washington, DC: US Dept of Agriculture, 1982.
- National Research Council. Evaluation of cyclamates and carcinogenicity. Washington, DC: Natl Acad Press, 1985.
- BUSBY WF, WOGAN GN. Aflatoxins. In: Searle CE, ed. Chemical carcinogens. Am Chem Soc Monogr 1984;182:945-1136.
- STOLOFF L. Aflatoxin control: past and present, J Assoc Off Anal Chem 1980:6:1067-1073.
- Leung AY. Encyclopedia of common natural ingredients. New York: Wiley, 1980.
- Tuyns AJ. Alcohol. In: Schottenfeld D, Fraumeni JF Jr, eds. Cancer epidemiology and prevention. Philadelphia: Saunders, 1982:293-303.
- Distilled Spirits Council of the United States. Public revenues from alcohol beverages. Washington, DC: DISCUS, 1981. San Francisco: Wine Institute economic research report. CA: Wine Institute, 1983.
- TOTH B. ERICKSON J. Cancer induction in mice by feeding of the uncooked cultivated mushroom of commerce Agaricus bisporus. Cancer Res 1986;46:4007-4011.
- TOTH B. Mushroom hydrazines: occurrence, metabolism, carcinogenesis, and environmental implications. In: Miller EC, ed. Naturally occurring carcinogens, mutagens, and modulators of carcinogenesis. Tokyo: Japan Sci Soc 1979:57-65.
- PREUSSMANN R. Occurrence and exposure to N-nitroso compounds and precursors. In: O'Neill IK, Von Borstel RC, Miller CT, et al. eds. n-Nitro compounds: occurrence, biological effects and relevance to human cancer. Lyon, France: IARC, 1984:3-15.
- CHOI BCK. N-nitroso compounds and human cancer. Am J Epidemiol 1985;121:737-743.
- SEN NP, SEAMAN S, MILES WF. Volatile nitrosamines in various cured meat products: effects of cooking and recent trends. J Agr Food Chem 1979;27:1354-1357.
- SCANLAN RA. Formation and occurrence of nitrosamines in food. Cancer Res 1983;43:2435S-2440S.
- International Agency for Research on Cancer. Some industrial chemicals and dyestuffs. IARC Monogr Eval Carcinog Risk Chem Hum 1982;29:93-148; 345-389.
- LONNEMAN WA, BELLAR A, ALTSHULLER AP. Aromatic hydrocarbons in the atmosphere of the Los Angeles basin. Environ Sci Technol 1968:2:1017-1020.
- 95. National Academy of Science. Benzene in air. Washington, DC: Natl Acad Press, 1980.
- Hunt WF Jr. FAORO RB, FREAS W. Report on the interim data base for state and local air toxic volatile organic chemical measurements. Washington, DC: EPA, 1986 [publication No. (EPA) 450/4 86 012].
- International Agency for Research on Cancer. Some halogenated hydrocarbons. IARC Monogr Eval Carcinog Risk Chem Hum 1979;20:371-399.
- LILLIAN D, SDIGH HB, APPLEBY A, et al. Atmospheric fates of halogenated compounds. Environ Sci Technol. 1975;9:1042-1048.
- LOVELOCK JE, MAGGS RJ, WADE RJ. Halogenated hydrocarbons in and over the Atlantic. Nature 1973;241:194-196.
- 100. HANST PL, SPILLER LL, WATTS DM, et al. Infrared measurement of fluorocarbons, carbon tetrachloride, carbonyl sulfide, and other atmospheric trace gases. J Air Pollut Control Assoc 1975;25:1120-1226.
- SINGH HB, FOWLER DP, PEYTON TO. Atmospheric carbon tetrachloride: another man-made pollutant. Science 1976;192:1231-1234.
- 102. ARTHUR RD, CAIN JD, BARRENTINE BF. Atmospheric levels of pesticides in the Mississippi Delta. Bull Environ Contam Toxicol 1976;15:129-134.
- STANLEY CW, BARNEY JE, HELTON MR, et al. Measurement of atmospheric levels of pesticides. Environ Sci Technol 1971;5:430–435.
- SINGH HB, SALAS LJ, SMITH AJ, et al. Measurements of some potentially hazardous organic chemicals in urban environments. Atmos Environ 1981;15:601-612.
- SINGH HB, SALAS LI, STILES RE. Distribution of selected gaseous organic mutagens and suspect carcinogens in ambient air. Environ Sci Technol 1982;16:872-880.
- 106. PATTERSON RM, BORNSTEIN ML, GARSHICK E. Assessment of formalde-

- hyde as a potential air pollution problem, vol 8. Bedford, MA: EPA, 1976.
- KITCHENS RD, CASNER RE, EDWARDS GS, et al. Investigation of selected potential environmental contaminants: formaldehyde, Washington, DC: EPA [publication No. (EPA)560/2-76-009].
- Versar Inc. Human exposure to formaldehyde. Draft report (contract No. 68-01-5791 for Office of Pesticides and Toxic Substances, Environmental Protection Agency, Springfield, VA), 1980.
- ronmental Protection Agency, Springfield, VA), 1980.

 109. CLEVELAND WS, GRAEDEL TE, KLEINER B. Urban formaldehyde: observed correlation with source emissions and photochemistry. Atmos Environ 1977;11:357-360.
- 110. KUTZ FW, YANG HSC. A note on polychlorinated biphenyls in air. In: Proceedings of the national conference on polychlorinated biphenyls, Chicago, 1975. Washington, DC: EPA, 1976:182 [publication No. (EPA)560/6-75-004].
- EISENREICH SJ, LOONEY BB, THORNTON JD. Airborne organic contaminants in the Great Lakes ecosystem. Environ Sci Technol 1981;15:30-38.
- 112. EISENREICH SJ, LOONEY BB, HOLLOD GJ, PCBs in the Lake Superior atmosphere 1978-80. In: Mackay D, Paterson S, Eisenreich SJ, et al. eds. Physical behavior of PCBs in the Great Lakes. Ann Arbor, MI: Ann Arbor Sci. 1983:115-125.
- 113. International Agency for Research on Cancer. Some halogenated hydrocarbons. IARC Monogr Eval Carcinog Risk Chem Hum 1979:20:491-514.
- 114. SINGH HB. Phosgene in the ambient air. Nature 1976;264:428-429.
- LIVINGSTON JM, JONES CR. Living area contamination by chlordane used for termite treatment. Bull Environ Contam Toxicol 1981;27:406-411.
- 116. WRIGHT CG, LEIDY RB. Chlordane and heptachlor in the ambient air of houses treated for termites. Bull Environ Contam Toxicol 1985;28:617-623.
- FENSKE RA, STERNBACH T. Indoor air levels of chlordane in residences in New Jersey. Bull Environ Contam Toxicol 1987;39:903-910.
- 118. LOUIS JB, KISSELBACH KC JR. Indoor air levels of chlordane and heptachlor following termiticide applications. Bull Environ Contam Toxicol 1987;39:911-918.
- CONNOR TH, THEISS JC, HANNA HA, et al. Genotoxicity of organic chemicals frequently found in the air of mobile homes. Toxicol Lett 1985;25:33-40.
- SCHAFER ML, PEELER JT, GARDNER WS, et al. Pesticides in drinking water: waters from the Mississippi and Missouri rivers. Environ Sci Technol 1969;12:1261-1269.
- WILLIAMSON SJ. Epidemiological studies on cancer and organic compounds in U.S. drinking water. Sci Total Environ 1981;18:187-203.
- 122. WILLIAMS DT. Formation of trihalomethanes in drinking water. In: Fishbein L, O'Neill IK, eds. Environmental carcinogens: selected methods of analysis, vol 7 (IARC publications No. 68), Lyon, France: IARC, 1985:69-88.
- 123. Environmental Protection Agency. Tolerance assessment system. Annualized chronic consumption data based upon the United States Department of Agriculture 1977 nationwide food consumption survey. Washington, DC: EPA, Office of Pesticide Programs, 1987.
- 124. COHEN DB, BOWES GW. Water quality and pesticides: a California risk assessment program, vol I. Sacramento, CA: State Water Resources Control Board (Toxic Substances Control Program), 1984.
- Environmental Protection Agency. Ethylene dibromide (EDB) position document 4. Washington, DC: EPA, Sept 27, 1983.
- SANDHU SS, WARREN WJ, NELSON P. Pesticidal residue in rural potable water. J Am Water Works Assoc 1978;70:41–45.
- 127. DENNIS DS. Polychlorinated biphenyls in the surface waters and bottom sediments of the major drainage basins of the United States. In: Proceedings of the national conference on polychlorinated biphenyls, Chicago, 1976. Washington, DC: EPA, 1976:183-194 [publication No. (EPA)560/6-75-004].
- 128. New Jersey Department of Environmental Protection. Results of testing for hazardous contaminants in public water supplies under Assembly Bill A-280. Final report. Trenton: NJDEP, 1987.
- 129. International Agency for Research on Cancer. Some halogenated hydrocarbons. IARC Monogr Eval Carcinog Risk Chem Hum 1979:20:545-572.
- American Water Works Association. Materials for research workshop on volatile organic chemicals. Denver: AWWA, 1972.
- 131. International Agency for Research on Cancer. Some monomers, plastics and synthetic elastomers, and acrolein. IARC Monogr Eval Carcinog Risk Chem Hum 1979;19:439-459.
- 132. California Department of Health Services. Organic chemical contam-

- ination of large public water systems in California. Sacramento, CA: CDHS, 1986.
- Environmental Protection Agency. Ambient water quality criteria for benzene. Washington, DC: EPA, 1980 (publication No. (EPA) 440/5-80/0181.
- 134. RUNION HE, SCOTT LM. Benzene exposure in the United States 1978-1983; an overview. Am J Ind Med 1985;7:385-393.
- 135. National Institute for Occupational Safety and Health. Criteria for a recommended standard. Occupational exposure to formaldehyde. Washington, DC, US Govt Print Off, 1976 [DHEW publication No. (NIOSH) 77-1251.
- 136. National Academy of Sciences. Formaldehyde: an assessment of its health effects. Prepared for the Consumer Products Safety Commission. Washington, DC: Natl Acad Sci Press. 1980.
- 137. SIEGEL DM, FRANKOS VH, SCHNEIDERMAN MA. Formaldehyde risk assessment for occupationally exposed workers. Regul Toxicol Pharmacol 183;3:355-371.
- 138. Bernstein RS, Stayner LT, Elliott LJ, et al. Inhalation exposure to formaldehyde: an overview of its toxicology, epidemiology, monitoring and control. Am Ind Hyg Assoc J 1984;45:778-785.
- Environmental Protection Agency. Technical document. Formaldehyde. Washington, DC: EPA, Office of Pesticides and Toxic Substances, November 16, 1981.
- FLINN FB. Industrial exposures to chlorinated hydrocarbons. Am J Med 1946;1:388–394.
- KLEINFELD M, TABERSHAW IR, Trichloroethylene toxicity. AMA Arch Ind Hyg 1954;10:134–141.
- 142. KIMBROUGH RD, MITCHELL FL. HOUK VN. Trichloroethylene: an update. J Toxicol Environ Health 1985;15:369-383.
- 143. SILBERGELD E. Risk assessment. Science 1987:237:1399.
- 144. BROWN HS, BISHOP DR, ROWAN CA. The role of skin absorption as a route of exposure for volatile organic compounds (VOCs) in drinking water. Am J Public Health 1984;74:479-484.
- 145. New York State Department of Health. A risk assessment for ethylene dibromide. Bureau of Toxic Substance Assessment, NYSDH, Feb 21, 1984

- WILLIAMS GM, WEISBURGER JH. Carcinogen risk assessment. Science 1983;221:6.
- 147. International Agency for Research on Cancer. Approaches to classifying chemical carcinogens according to mechanism of action. Lyon. France: IARC, 1983 (technical report No. 53:001).
- 148. WEINSTEIN IB. Letter to the editor. Science 1983;219:794-796.
- PERERA F. The genotoxic/epigenetic distinction: relevance to cancer policy. Environ Res 1984;34:175-191.
- 150. Office of Science and Technology Policy. Chemical carcinogens: review of the science and its associated principles. Federal Register. March 14, 1985;50:10372-10442.
- 151. California Department of Health Services. Guidelines for chemical carcinogen risk assessments and their scientific rationale. Sacramento. CA: CDHS, 1985.
- 152. KOCIBA RJ, KEYES DG, BEYER JE. Results of a two-year chronic toxicity and oncogenicity study of 2,3,7,8-tetrachlorodibenzo-p-dioxin in rats. Toxicol Appl Pharmacol 1978;46:279-303.
- 153. National Toxicology Program. Carcinogenesis bioassay of 2.3.7.8-tetrachlorodibenzo-p-dioxin in Osborne Mendel rats and B6C3F, mice (gavage study). Research Triangle Park, NC: NTP, 1982 (technical report No. 209).
- PITOT HC, GOLDSWORTHY T, CAMPBELL HA, et al. Quantitative evaluation of the promotion by 2.3.7.8-tetrachlorodibenzo-p-dioxin of hepatocarcinogenesis from diethylnitrosamine. Cancer Res 1980;40:3616– 3620.
- POLAND A, PALEN D. GLOVER E. Tumor production by TCDD in skin of HRS/J hairless mice. Nature 1982;300:271.
- 156. International Agency for Research on Cancer. Genetic and related effects: an update of selected IARC monographs, vol 1-42. IARC Monogr Eval Carcinog Risk Chem Hum (suppl 6). In press.
- 157. WATERS MD, STACK HF, BRADY AL, et al. Use of computerized data listings and activity profiles of genetic and related effects in the review of 195 compounds. Mutat Res 1988:205:295-312.
- 158. DAY NE, Brown CC. Multistage models and primary prevention of cancer. JNCI 1980;64:977-989.

Acceptable Cancer Risks: Probabilities and Beyond

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The acceptability of cancer risk requires consideration of factors that extend beyond mere numerical representations, such as either individual lifetime risk in excess of background and excess incidence. Recently, use of these numbers has been tempered by the addition of qualitative weights-of-evidence that describe the degree of support provided by animal and epidemiologic results. Nevertheless, many other factors, most of which are not quantitative, require incorporation but remain neglected by the analyst eager to use quantitative results.

In this paper we show that simple risk measures are often fraught with problems. Moreover, these measures do not incorporate the very essence of acceptability, which includes notions of responsibility, accountability, equity, and procedural legitimacy, among others. We link the process of risk assessment to those legal and regulatory standards that shape it. These standards are among the principal means to resolve risk-related disputes and to enhance the balancing of competing interests when science and law meet on uncertain and often conjectural ground.

We conclude the paper with a proposal for the portfolio approach to manage cancer risks and to deal with uncertain scientific information. This approach leads to the concept of "provisional acceptability," which reflects the choices available to the decisionmaker, and the trade-offs inherent to such choices.

Agencies, industry, and the public demand clear standards for judging the acceptability of risks. Numerical values could reduce debate and ambiguity, clarify the responsibilities of businesses, and provide data for regulatory, judicial, and legislative deliberations.^{1,2}

Recognizing that a single risk level is not appropriate in all contexts, it is tempting to propose specific numerical "ac-

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ceptability" values for different classes of risks. For example, the average acceptable excess individual lifetime fatality probability of cancer from occupational exposures (assuming full disclosure and informed consent) might be set at 1×10^{-4} . A level of $1.\times 10^{-6}$ could be defined as acceptable for the general public experiencing involuntary exposures. A much higher risk level, such as 1×10^{-3} , might be appropriate for sales of inherently dangerous products to fully informed, willing customers. Aggregate incidence could be acceptable if it were less than some value, for example, unity. However, even such a range of numbers over different contexts is neither conceptually adequate nor sufficient as a basis for responsible decisionmaking.

Whether a risk is "acceptable" generally depends not only on its objective quantitative probability and the nature and severity of the consequences, but also on societal and political factors. Single numerical estimates of individual and population risks do not incorporate those qualitative aspects of risk. Protection of individual rights, the equity of risk-benefit distribution, prudence when facing uncertainty, the absence of knowledge, the legitimacy of the risk management process, and public attitudes toward and perceptions of risks do not lend themselves well to bare numerical representations 4

This paper examines these issues, assesses some current approaches to social and legal risk management, and proposes a risk-portfolio approach in which risk acceptability is an evolving concept. We begin with three concepts of risk.

Individual and Population Risks

Two related concepts are useful in describing risk to an individual: the *total risk* to an individual of a particular adverse health consequence, such as cancer; and the concept of an *attributable risk* describing the incremental contribution to total risk made by a particular source or cause (e.g., the contribution made by cigarette smoking to the risk of lung cancer). Finally, we discuss *population risk*, in which individual risk is aggregated over the population at risk.

Total Individual Risk

The total risk to an individual of developing some undesirable health response, such as death from cancer, may be defined as the probability that he will develop the response in a given year t, if he has survived until then. This probability is also called the individual's discrete time "hazard rate"

for the response in year t. Hazard rates can be used to calculate probabilities of cause-specific deaths or illnesses, to derive survival time probability distributions, and to quantify total risks over time. 5,6 Individual hazard rates for chronic health effects typically depend on the exogenous factors to which an individual has been exposed, including the extent of exposure to a particular chemical or radiation. Endogenous factors such as the efficiency of the body's repair mechanisms, genetic predisposition toward response, and so forth, may also affect individual hazard functions. Endogenous factors mediating between exposures and health responses usually vary widely across individuals and often cannot be observed. Thus, individual responses to specific exposures are quite heterogeneous. Even if an individual knew his own exposure history to a chemical, he would generally remain uncertain about his own future hazard function, and hence, about his probability of adverse re-

A problem often overlooked in discussing risk numbers is that interpreting them in terms of expected annual frequencies, or average times until occurrence, can be misleading. For example, a leukemia hazard rate from exposure to benzene in the workplace of one expected excess case per million person-years of exposure does not imply that the probability of a randomly selected worker developing cancer from a year of exposure is 1×10^{-6} . For any individual, it is considerably more likely than not that the actual waiting time to the first arrival will be less than the average (or "expected") waiting time.⁵ The probability that a randomly selected individual will develop cancer from a year of exposure is actually 6.3 × 10⁻⁵. The actual individual risk may thus exceed what was believed to be acceptable under a simple regulatory scheme that requires acceptable exposure to be determined from an average risk of, say, 1×10^{-6} .

Attributable Risk

In practical risk assessment and management, the problem is not how to estimate an individual's total risk of some health response, but how to estimate the incremental contribution to his risk made by some particular cause or source. This is the risk that is said to be attributable to the source. ^{6,7} Few concepts in risk analysis have occasioned as much perplexity and debate as that of the risk attributable to a source. ^{8,9}

One elementary model that can clarify the meaning of attributability postulates that each source of risk "competes" with other sources to be the first to cause an adverse response. Suppose that N sources contribute to the risk in an individual. Each source can be thought of as firing a random stream of biologically effective molecules that cause "hits" in the exposed individual. The average arrival rate or intensity of hits from source i at time t is the source's hazard rate at time t, denoted by $h_i(t)$. If the N potential sources of a health effect are statistically independent so that the arrival rate of hits from one source is unaffected by the presence of other sources, then the total risk to the individual at time t from all sources is given by the sum $h(t) = h_i(t) + \ldots + h_n(t)$. Since any source i will contribute the fraction $h_i/h(t)$ of all expected hits per unit time at time t, this ratio equals the probability that source i contributed the hit that caused the observed health response, and $h_i(t)$ is the risk attributable to source i at time t.

This "competing risk" definition of attributable risk is satisfactory only when the random arrival model correctly represents the nature of causation. For example, suppose that occurrence of a health effect depends on whether the total number of hits received from all sources within a certain amount of time exceeds a certain threshold. Then, if a response occurs, it cannot even in principle be ascribed to any single source. ¹⁰ Similarly, if the presence of factor A doubles the hazard rate from factor B, then a hit from B may

be partly blamed on A. In such cases of joint and multiple causation, assignment of shares of causation to the different contributing sources is as much a matter of policy as one of science. 8,10

Population Risk

Individual risks are not sufficient to determine the effect that a risk management choice can have on those at risk. The full impact of a choice can only be evaluated by looking at the *distribution* of effects in the affected population as a whole.

If the population at risk consists of several "types" of individuals, with each type corresponding to a homogenous subpopulation of individuals having identical hazard functions for death from cancer, then in each homogenous subpopulation the amounts of time (number of life-years) that the members have left until death will be statistically independent, identically distributed random variables. At any time, the total number of remaining life-years in the population, summed over all the individuals now in it, will be approximately normally distributed, with mean and variance equal to the sums of the means and variances, respectively, of the remaining life-years in each subpopulation. The problem of evaluating population risk in large populations can thus be reduced to the problem of evaluating normal distributions for the attribute "remaining life-years in the population." This is a standard decision-analytic problem.11-13

If an individual considers himself to be a randomly selected member of the population, then his individual risk is the expected value of the risks for all individuals in the population. There is a paradox: if two different population risk distributions have identical means, then every individual should be indifferent among them (based on his own expected risk). But the distributions may not be equally desirable from a societal perspective. In fact, a variety of different distributions of risks and uncertainties can occur at the population level. It is not the expected number of occurrences per million person-years of exposure in the whole population that counts in determining equity, but the way this risk density is distributed among identifiable subgroups of the population. Consider choosing among the following situations:¹⁰

Case A (Uniform population risk): Each of 100 people independently is exposed to a 0.01 chance of disease.

Case B (Anonymous sensitive subpopulation): 10 of the 100 people are exposed to a 0.10 chance of disease. The rest have a zero chance of disease. Now one knows which type he is unless and until he gets the disease.

Case C (Known high risk population): 50 of the 100 people (e.g., neighbors living within a certain distance of an industrial facility) are at high risk and know it. Each of these individuals has a 0.02 probability of disease; the remaining 50 people have zero risk.

Case D (Uncertain individual risk): Each individual has a random probability, independently drawn from a uniform distribution between 0 and 0.02, of getting the disease.

Case E (Uncertain population risk): Each individual independently has the same probability of getting the disease. The magnitude of this probability is uncertain; however, it is judged equally likely to be anywhere between 0 and 0.02.

Imagine trying to rank these situations in terms of relative social desirability. Simply using the expected number of casualties as a summary of population risk results in the same assessment of risk (one expected case) for all of these examples. Aggregating risk obscures uncertainties, heterogeneities, and inequities. The five cases involve important trade-offs: between number of people exposed and magni-

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tude of exposure per person, between certain and uncertain risks, and between equitably and inequitably distributed risks.

The concepts of individual and aggregate risks are quantitative expressions that, at best, summarize all relevant biological information. However important these concepts are, there are other social and ethical dimensions that also contribute to risk acceptability. For example, what constitutes an acceptable risk for one person to offer to another depends on both rights (e.g., the right of free choice to assume an otherwise "unacceptable" risk) and duties (e.g., the legal duty not to endanger others even with their consent).

Acceptability also depends on the responsibilities that acceptance entails. For example, an informed cancer patient, cognizent of the risks and uncertainties associated with a new, unlicensed chemotherapeutic drug, might consider its administration personally acceptable but not acceptable to administer to someone else. At the other extreme, the social decisionmaker faces accountability: if she regulates the specific risk by selecting a specific option, but other unknown risks eventually result from her choice, even though she may not have been responsible for those risks, she may be held socially accountable for them. The next section explores these concepts.

Attitudes Toward Risk

The issue of voluntary acceptance underlies many debates about acceptability in the context of making decisions about risks. In a society that values individual choice, a risk that an individual is willing to take for himself may be acceptable, even though a quantitatively similar risk imposed by another is not.

The concept of voluntary acceptance of risks has several important components. First, there are gradations of "volluntariness." A truly voluntary activity is one that an individual is free and able to reject without penalty, that he can control while undertaking, and whose risks are fully known or easily discoverable. Less clearly voluntary are activities that an individual is intially free to reject without penalty, but over which he loses some control over time. Drinking, smoking, and other addictive activities are examples. Voluntariness may be further compromised when advertisements and deliberate inducements play a major role in the initial decision to participate in the activity. ¹⁴

The appearance of controllability also plays a large role in individual judgments of risk acceptability. So does the belief that a truly free choice requires participants to have full information about what is being chosen. Right-to-know, need-to-know, and duty-to-warn legislation, as well as principles governing "adhesion" contracts, make clear the notion that lack of information about the risks in an economic transaction undermines one's consent to accept risk.

Individual perceptions and preferences regarding risks can be fragile, changeable, overly sensitive to initial impressions, and unreliable. This raises crucial questions for policymakers. When public perceptions and statistical realities conflict, is it the decisionmaker's duty to represent the views and preferences of members of society, or to protect what he considers to be in their true interests? How can a line be drawn between responsibility and paternalism when public preferences appear to be based on inaccurate perceptions? Does the judgment that a population risk is acceptable apply to the median, the average, the most highly susceptible, or the most risk-averse individual in the population?

In practice, the distribution of risks and risk perceptions within the population at risk is often left unexplored. Instead, the individual risk to the maximally exposed individual is given special attention by regulatory agencies. The assumption is that if risk to the maximally exposed individual is acceptably small, then the risk to the entire population

is plausibly also acceptable. However, as discussed above, this view is suspect: population risk and individual risk should be assessed separately. For example, a maximally exposed adult may have a hazard rate that is higher than a child's, even though both are identically exposed to a particular toxic chemical.

In addition, the alternative concept of a "maximally threatened" individual is poorly defined. For example, who is more "threatened," an individual whose hazard rate is increased from 0.01 to 0.02, or an individual whose hazard rate is increased from 0.02 to 0.03? The former faces 50 years of lost life expectancy (with it being considerably more likely than not that the loss will be greater than its expected value), while the latter faces only a 17 year reduction in life expectancy. On the other hand, with less expected life left, the second individual might be thought to suffer more for each additional expected year lost.

Procedural Legitimacy

Risk decisions usually involve numerous parties with conflicting interests. Individuals may be considered to have accepted a risk "voluntarily" if they "agree to" the decision-making process leading to it. Very often the perceived legitimacy of that process depends on the degree to which the risk-bearing public could participate in regulatory decisions. The history of nuclear power and hazardous facility siting in this country illustrates the close connection between perceptions of voluntary participation (or opportunity to participate) in judging risk acceptability, the perceived legitimacy of regulatory processes, and the acceptability of risks. 14,15

An individual may agree to abide by the results of a social decision process because she expects to gain from the process on average, even though she may lose from particular decisions. From this perspective, acceptability of each risky prospect is not the most relevant issue. Rather, the acceptability and equity of the entire portfolio of risks, selected through the process over time, are what matter. ¹⁶ We will develop this theme by examining the regulatory and judicial process by which our society's risk activity portfolio is largely determined in practice, with focus on its fairness when methods and results are at the frontiers of knowledge and when societal risks, economic costs, and benefits may be large.

Private Litigation

Private litigation over environmental injuries have been standard fare for hundreds of years. William Aldred, to take one well known example, successfully sued his neighbor for damages on the ground that the neighbor's pigsty "corrupted" the air and thereby prevented Aldred from living in his own home. The from these humble common law beginnings, courts and legislatures have developed a massive body of private law to compensate environmental injuries by awarding damages and to prevent future injuries through both injunctive relief and the deterrent effect of potential damage awards.

Although private litigation is no longer the principal means to regulate environmental injuries, it continues to play a potentially important role, especially with regard to its principal goals of compensation and deterrence. Private litigation is almost the sole means, other than first party insurance, to obtain monetary compensation for personal injuries and property damage, something that most regulatory schemes fail to do (although they could). In addition, many regulatory schemes are not comprehensive in scope; the legislature and the agency have failed to regulate (or failed to regulate adequately) significant environmental problems. In these cases, private litigation could supplement or fill in the gaps in existing regulatory programs.

Finally, nuisance and other tort doctrines often allow plaintiffs to secure prompt injunctive relief, such as a temporary restraining order, to prevent imminent injuries. A judge will grant relief after making an ad hoc balancing of the equities in the particular case. Under most regulatory schemes, by contrast, an injured or threatened citizen must first persuade a government official to seek injunctive relief from the court.

Despite the venerable origins of private environmental litigation, and its unique strengths, there are serious questions about the appropriateness of private remedies for polycentric social questions, and the capacity of courts to decide environmental tort cases. Although some of the following problems could be cured by legislative reforms, ^{18–20} others are more resistant.

Statutes of limitations. Statutes of limitations traditionally have posed an impassable obstacle to recovery if the injury does not manifest itself for many years. Many states, however, have reduced this obstacle by postponing the time limits for filing suit until the injury manifests itself or until the link between exposure and injury would be known to the "reasonable person," even though it may not be known to the actual plaintiff.

Litigation costs. Private litigation is expensive. Many lawyers are unwilling to undertake a private suit with a low and uncertain probability of success, even though the suit may have merit. The result is substantial undercompensation and reduced deterrent effect.

Complexity. Environmental problems often involve complex, uncertain, and sometimes unresolvable scientific issues. Is it realistic to expect that judges and juries will be able to intelligently address and resolve the technical and scientific questions when science cannot provide defensible answers? How will firms be able to make informed, long-term investments if the outcomes of cases are so uncertain?

Cases alleging environmental injury may take several years to resolve. In part, this is a result of the scientific complexity of the assumptions, theories, and data underlying the disputed factual issues. In part, lengthy delays occur because the judicial system does not have the administrative capacity to handle mass-injury cases, such as injuries from exposure to asbestos. More fundamentally, there has been a basic shift in the focus of tort law. Environmental tort cases today are not bipolar disputes, such as the one between William Aldred and his neighbor. Instead they affect:

great aggregations of people and vast economic and social interests. The decisions in these cases are preoccupied ... with advancing public control of large-scale activities and altering both the distribution of power and the nature of social values. In such cases, the parties are ... mere placeholders for these larger social interests.²¹

What should a court do if the requested injunctive relief would injure numerous persons who depend on the polluter for employment, taxes, and consumer products? Since these cases raise policy issues involving the allocation of resources among different segments of the community, should those issues be decided in court or left to the political process?

Causation. Causation may be an intractable issue in toxic tort law.²²⁻²⁵ There are really two causation problems, known as the indeterminate defendant and the indeterminate plaintiff.²¹ The indeterminate defendant problem occurs because in most cases there are numerous sources of pollution, which makes it difficult to directly identify the source (or sources) that caused the plaintiff's injury. Some courts have addressed this problem by apportioning liability among defendants through a market share theory, where the harm results from an identifiable product.²⁶ This approach has no applicability where the injury may have resulted from

a variety of ubiquitous chemicals dispersed through the environment, some of which act synergistically. The market share theory also may be of little help when, as is common in toxic torts, the injury manifests itself years after the injurious exposure occurred, and the potential plaintiffs have gone out of business or are difficult to identify.

The indeterminate plaintiff problem arises because many injuries (particularly injuries to health) are "nonsignature," meaning that the injuries could have resulted from a number of causes, some of which are natural. For example, although several members of the community may have evidence that the chemicals in the defendant's air emissions cause lung cancer, comparisons with other communities suggest that most of the lung cancer cases would have developed regardless of the defendant's polluting activity. In the Agent Orange case, which began in 1975 and concluded in 1984, the trial judge granted summary judgment to several chemical companies against non-settling plaintiffs, largely on the trial judge's conclusion that the plaintiffs had failed to establish this kind of causation. Although the court also approved a \$180 million settlement covering most plaintiffs, the court's approval was based more on sympathy for the veterans than on belief that they had demonstrated causation.^{27,28} The problem is easy to state but difficult to resolve:

identification, ordinarily a routine issue of cause in fact at common law, is a costly enterprise that relies on types of evidence and probability judgments which can be regarded as ill-suited to traditional resolution through the adversary process.²⁰

One problematic aspect of the indeterminate plaintiff issue is illustrated by the following example. Suppose there was a clear correlation between the defendant's polluting activity and a 15 percent increase in the expected number of lung cancer cases in the vicinity of the defendant's plant (of course, such correlations are almost never clear cut for nonsignature diseases), but that it was unclear which cases resulted from the defendant's air emissions. Should damages be awarded in full to every person with lung cancer? Or is the proper award to each person with lung cancer 1/115 of a sum of money representing damages for 15 cases (i.e., 15 full awards spread out over every 115 people with lung cancer)? It is doubtful in these circumstances that it is ever possible to avoid both overcompensation and undercompensation.

Agency Decisionmaking

In principle, a regulatory system should overcome many of the shortcomings of private litigation. Issues of expertise, complexity, political accountability, and causation should prove to be smaller obstacles. Nevertheless, pervasive scientific uncertainty, as well as the ambiguity inherent in statutory commands, make agency decisionmaking problematic as well.

A regulatory agency generally uses one of two processes to manage risks: administrative adjudication or rulemaking. Administrative adjudication is the case-by-case determination of regulatory issues, such as whether to cancel the registration of a particular pesticide. In adjudication, an administrative law judge presides over a formal, trial-type hearing and, after listening to evidence, formulates findings of law and fact. Rulemaking, by contrast, produces regulations governing the activities of entire industries. Most federal rulemaking proceedings under environmental and worker safety statutes do not employ live hearings, but instead rely on written submissions that constitute the administrative record. Generally, most agency policies and decisions concerning health and safety are generated through rulemaking proceedings.

One of the hallmarks of modern agency decisionmaking in the United States is extensive public participation.²⁹ Before adopting a regulation, for example, the agency must publish

the proposed regulation, a summary of the reasons and factual bases for the regulation, and the time and place for submitting written comments. Anyone may submit written comments, reports, data, or objections related to the agency's proposed rule, and any documents submitted to the agency are available for public review. In publishing a final regulation, the agency must explain the basis for the rule, including any changes from the proposed rule, and must respond to (but need not rely on) all material comments and objections.

Public participation serves multiple, sometimes conflicting purposes. At one level, public participation legitimates agency decisionmaking. Many agency decisions are controversial because there are not adequate data leading unambiguously to a single policy choice. Such decisions are necessarily value-laden. Public participation, coupled with the requirement that the agency take seriously and respond to all material comments, can ensure that all interested parties have roughly equal access to political decisionmaking, and thus can help to ensure at least a minimal level of public accountability by agency officials.

At another level, unrestricted public participation may also help to ensure that the agency has made the "best" decision. By being required to consider all points of view, the agency is much less likely to overlook relevant data or perspectives, and also is more likely to be able to overcome its institutional biases.³⁰

In addition to procedural constraints on agency decisionmaking, the legislature also sets the substantive criteria for agency regulations in virtually all risk management statutes. One characteristic of modern environmental and worker safety statutes is their relative specificity.

The two extremes of pollution control standards are "health-based" and "technology-based" standards. An example of a "health-based" standard is section 112 of the Clean Air Act. Under that provision, the Administrator of the Environmental Protection Agency must set a hazardous air pollutant standard that "in his judgment provides an ample margin of safety to protect the public health." The current judicial interpretation of this language prohibits the Administrator from considering implementation costs or technological feasibility in setting an "acceptable" or "safe" level of risk.31 After fixing this "safe" risk level, the agency must further reduce the emission rate (to add the statutory ample margin of safety) to the extent permitted by implementation costs and technological feasibility. Thus, under this interpretation, even the best available control technologies do not necessarily meet the statutory standard.

Not surprisingly, this interpretation has caused consternation in regulatory circles, for it requires the agency to determine a level of acceptable risk wholly out of context; implementation costs and technological feasibility ostensibly are irrelevant to the agency's initial determination of acceptable risk. There is some reason to believe that the EPA will seek to circumvent the statutory restriction. The agency recently proposed to define acceptable risk as equivalent to a maximum individual lifetime risk in the neighborhood of 1×10^{-4} . The precise number would vary depending on unspecified factors; in one example, the risk level was 6 × $10^{-3.32}$ By proposing a relatively high level of acceptable risk—one that few people would define as acceptable—EPA effectively would be able to give much greater weight to costs and feasibility considerations than if it had begun with a more conventional estimate of acceptable risk.

An example of a "technology-based" standard is section 111 of the Clean Air Act. That provision requires the EPA Administrator to set emission standards for new sources of nonhazardous air pollutants that "reflect the degree of emission limitation...achievable through application of the best technological system... which (taking into consideration the cost of achieving such emission reduction...) the Administrator determines has been adequately demonstrated."

Thus, in contrast to section 112, section 111 requires EPA to consider implementation costs and the availability of technological controls in setting emission standards.

As these two examples illustrate, the substantive statutory language often is imprecise, and thus leaves the agency considerable room for interpretation. How expansive is the definition of "public health"? Should the standards be set to protect every vulnerable individual, no matter how hypersensitive? If not, where should the line be drawn? How much of a margin is an "ample margin of safety"? How should the Administrator "consider" costs under section 111? How should the Administrator determine what is the "best" system of pollution control? When is a technological control system "adequately demonstrated"? Plainly, in these provisions the legislature has only defined the broad outlines of regulatory policy. Crucial substantive details remain to be worked out in agency rulemaking proceedings.

Despite the inherent ambiguity of the statutory language, however, it is evident that the health-based and technology-based criteria represent two very different approaches to the regulation of human health risks. Even though the statutory language leaves the agency considerable policymaking discretion, these criteria impose important limits on the ambit of agency authority. Health-based criteria require the regulator to focus exclusively on health risks—e.g., their nature, magnitude, and distribution—in determining acceptable emissions standards. Technology-based criteria, by contrast, require the regulator to focus entirely on the availability and cost of pollution control technology. Thus, the legislature, through the substantive statutory criteria for pollution standards, defines the factors that contribute to a determination of acceptable risk in different circumstances.

Judicial Review

A critical element of the rulemaking process is judicial review. Roughly speaking, judicial review is designed to ensure that the agency has conformed to the statute's procedural and substantive requirements. If the agency failed to comply with the statutory requirements, the court would remand the case to the agency for reconsideration in compliance with the statute. The policy goal of widespread public participation in agency decisionmaking is advanced here by statutes and doctrines permitting any person to seek judicial review of agency actions.

Ensuring that the agency has conformed to the procedural requirements is essential to any notion of public participation and agency accountability. Without adequate judicial review, agency officials would be free to disregard conflicting perspectives and to make policy choices without a thorough public airing. For example, in the course of deciding not to regulate formaldehyde under the Toxic Substances Control Act, EPA officials held private meetings with representatives of industry.³³ As a result, opposing views were largely left out of the decisionmaking process, EPA deviated arbitrarily from the existing cancer policy guidelines, and the agency did not follow procedures for internal review of policy decisions. Judicial review of agency procedures could have helped ensure the legitimacy and integrity of the quasipolitical process that is central to agency rulemaking.

More commonly, judicial review focuses on whether the agency's substantive decision conforms with the statutory criteria. Inevitably, this issue is linked with questions involving the extent to which the reviewing court should defer to the agency's interpretation of the statute, and the degree to which the court should probe the validity of the agency's technical judgments.

The courts' willingness to read statutes instrumentally, and thus to disregard agency interpretations, was illustrated in *Industrial Union Dep't*, AFL-CIO v. American Petroleum Institute.³⁴ In that case, a plurality of the Supreme Court remanded the OSHA benzene exposure standard of 1

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ppm to the agency for reconsideration. The Court's decision was based on its reading of a convoluted statute as requiring the agency to show that the health risks to workers were "significant," a word that does not appear in the statute. It is plain from the Court's opinion that its interpretation was driven by concerns that OSHA's interpretation would result in excessively strict regulations.³⁵

More recently, the federal courts have assumed a deferential posture toward agency interpretation of regulatory statutes. In a series of cases over the last five years, the Supreme Court has emphasized that for reasons of political accountability and technical expertise, regulatory agencies have the primery responsibility for interpretation. In a case discussing EPA's interpretation of one section of the Clean Air Act, the Court wrote:

the regulatory scheme is technical and complex, the agency considered the matter in a detailed and reasoned fashion, and the decision involves reconciling conflicting policies... Judges are not experts in the field, and are not part of either political branch of the Government.... When a challenge to an agency construction of a statutory provision, fairly conceptualized, really centers on the wisdom of the agency's policy, rather than whether it is a reasonable choice within a gap left open by Congress, the challenge must fail.³⁶

Nevertheless, some scholars condemn the courts' default in favor of agency interpretation of statutes, ^{37,38} and thus in favor of agency policymaking authority. Other authors, however, insist that agencies are politically accountable and thus in the best position to make the policy decisions inherent in statutory interpretation. ^{39,40}

Of course, if the statute is fairly clear, a court will not allow an agency to disregard the statutory language, even though the statute vastly overregulates the risks. A good example of this occurred when a court reviewed an FDA decision to list as safe the color additives Orange No. 17 and Red No. 19, which are used in cosmetics. Although the agency determined, through animal bioassays, that these color additives were carcinogenic, 41 the calculated risk assessments showed that No. 17 would increase individual lifetime excess cancer risk by 2×10^{-10} , and No. 19 by 9×10^{-6} . The FDA concluded that these risks were too trivial to regulate. Indeed, there was some precedent to suggest that agencies possess an inherent statutory authority to disregard "de minimis" or trivial risks.43 Unfortunately, this decision apparently conflicted with the express words of the Delaney Clause of the Food, Drug and Cosmetic Act, which prohibits all color additives that "induce cancer in man or animal." The court in Public Citizen v. Young recognized that the clause was "extraordinarily rigid," but it reluctantly adhered to the statutory wording.48

The other area of substantive judicial review involves the agency's judgment that a regulatory standard satisfies the "significant risk," "ample margin of safety," or some other statutory criterion. Under many statutes, a court may remand an agency decision only if it is "arbitrary, capricious or an abuse of discretion." Other statutes require the agency to show that its decision is supported by "substantial evidence." In interpreting these somewhat ambiguous standards the federal courts often have melded them into a single "hard-look" doctrine, which is a collection of techniques to control agency discretion. Under the doctrine, an agency decision can survive judicial review only if the agency has given a reasoned explanation of the bases for its decision, supported its decision with substantial evidence, explored alternatives, given reasons for rejecting the alternatives, and responded to public criticisms and objections.44

In determining whether the agency's decision is supported by substantial evidence, it is enough "that the administrative record contain(s) respectable scientific authority" supporting the agency's factual findings. 45 The Supreme Court has written:

It is the Agency's responsibility to determine, in the first instance, what it considers to be a "significant" risk.... OSHA is not required to support its finding that a significant risk exists with anything approaching scientific certainty.... Thus, so long as they are supported by a body of reputable scientific thought, the Agency is free to use conservative assumptions in interpreting the data with respect to carcinogens, risking error on the side of overprotection rather than underprotection.⁴⁶

Even where there are no data, or the data sharply conflict, a reviewing court will uphold the agency's policy judgments if the agency explains the considerations it relied on. In Industrial Union Dep't, AFL-CIO v. Hodgson, for example, the court readily upheld OSHA's decision to delay a new asbestos standard. Given the conflicting scientific views of the health impact of the delay, as well as the statutory policy to adopt feasible standards, the court held that the delay was not irrational.⁴⁷ Similarly, in Building & Construction Trades Dep't, AFL-CIO v. Brock, the court was unwilling to second-guess OSHA's finding that certain asbestos exposure levels posed a "significant risk" to workers.⁴⁸ In short, the courts generally defer to the agency's technical and administrative expertise even though the agency rationally might have made other, perhaps better, decisions.⁴⁹

Inevitably, however, close judicial review of the agency's reasoning gives a court considerable opportunity to express its own substantive policy preferences. By immersing itself in the technical evidence, and determining whether the agency decision was "rational," the court often will not be able to avoid substituting its own views on the merits of the underlying issue. This may be especially true when the scientific evidence is most controverted. For example, in Asbestos Information Ass'n v. OSHA, the court reluctantly accepted the agency's assertion that an estimated eighty deaths, out of a worker population of 375,000, would constitute a "grave risk" that would justify an emergency temporary standard for asbestos exposure. Based on the court's own examination of the record, however, the court concluded that the numerical estimate was speculative and thus insufficient to support the agency's finding. As a result, the court stayed enforcement of the agency's emergency temporary standard. 50 Perhaps because it fears that lower courts will routinely intrude on agency policymaking authority, the Supreme Court in another case admonished that when reviewing agency decisions are "at the frontiers of science...a reviewing court must generally be at its most deferential."51 Acceptability is more than probabilities and scientific assessments; it results from a decisionmaking process that ison average-fair. When also viewed in the context of a portfolio of risks, the process tends to avoid ad hoc solutions.

The Portfolio Approach to Risk Acceptability

As illustrated in the preceding cases, risk assessment is based on a flux of scientific information concerning often highly uncertain or speculative risks. New knowledge, improved ability to control risks, and changes in risk attitudes can make a formerly acceptable risk no longer acceptable. Decisions about risk acceptability are thus dynamic and provisional; they must be monitored and adapted over time. For a regulatory agency, the acceptability of a specific risky activity depends on the context of other activities and control opportunities in which it is embedded. This view provides a new perspective for integrating risk acceptability issues into a framework for organizing social risk management decisions.⁵²

An agency's approach to risk management can be viewed in terms of its management of four sets of risky activities. One set contains *known* problems waiting for regulation. A second set consists of *suspected* problems requiring further

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investigation and possibly action. Finally, there are two disposition sets: one of solved problems that have been investigated and for which regulatory solutions have been established that must now be monitored and enforced; and one for nonproblems that have been investigated and found not to be problems. The known and suspected problem sets are sorted in order of decreasing priority of the problems in them, forming two rank-ordered lists. As suspected problems are investigated, and uncertainties about their risks are resolved, they change positions in the list for suspected problems. They may be moved down and off the suspected problem list altogether and onto the nonproblem list, or they may be moved up until they are pushed off the suspected problem list and inserted into the known problem list.

Risk management can be viewed as allocating resources to resolving problems on the two different action lists. In each budget period, the agency must allocate its resources to problems on the known and suspected lists. This requires trade-offs. Is it better to spend resources addressing another known problem or investigating another suspected one? When do the unknown risks from failing to explore items on the suspected problems list outweigh the losses from deferring action on known problems? And how should the pending problems within each list be ordered in terms of priority?

The only permanently acceptable risks are those moved to the nonproblem set. However, within any given period of time, there are known and suspected problems that are so far down on their corresponding priority sets that they will not be addressed until long after the many higher-priority problems that dominate them have been resolved. Such problems pose provisionally acceptable risks: risks that are acceptable until more important ones have been resolved.

In practice, new problems for investigation and resolution are continually being created by industrial society as new products and technologies emerge. Each new problem or potential problem requires positioning it, in the appropriate priority position, on the known problem or suspected problem list. If the rate at which high-priority problems are generated is greater than the rate at which they can be investigated, then existing problems will remain provisionally acceptable.

Of course, the process of setting the regulatory agenda is not as simple as this brief description suggests. Many problems are put on the public agenda as a result of the political and legal efforts of opposing parties. Rather than agency pull, in which problems are actively sought out for investigation to protect the public, public push may bring risk management problems onto the judicial, administrative, or legislative agenda. Episodic crises, such as the Bhopal disaster, also strongly affect the regulatory priorities regardless of the agency's assessment of their significance.

Although, in principle, toxic tort litigation can be included in the portfolio approach, the jurisdictional peculiarities of tort disputes stemming from state sovereignty, as well as the decentralized trial court system, prevent a centralized management of risks. This is less of a problem in the federal judicial system. Nevertheless, even though federal multidistrict litigation is possible, as the Agent Orange case demonstrates, tort law has a different focus than agency rulemaking under a risk management statute. Tort law emphasizes private, individual and class protection. Its objectives are principally compensation and to a lesser extent deterrence and occasionally punishment. Environmental statutes and agency rulemaking, by contrast, seek to prevent public injuries by enforcing standards adopted through a mixed political and technocratic process that may emphasize administrability as much as public health protection. Given these different objectives, it would be odd if the portfolio approach were equally applicable to both risk management systems.

The portfolio approach may also be inapplicable to toxic tort litigation because the individual risks, costs, and poten-

tial benefits of a case may differ from the societal ones. For example, since many of the costs of toxic tort disputes are borne by the affected parties, individual perceptions of risks, benefits and costs will affect the selection of disputes for litigation. The individual benefits of winning a case may be smaller than, or different from, the social benefits so that litigation that might be socially worthwhile may not be undertaken.⁵³ As a result, the portfolio approach is most difficult to apply to private litigation. Thus, social risk management by private litigation is a complement to, rather than a substitute for, risk management by regulatory agencies.

The concept of a portfolio of risks is also useful for companies whose allocation of resources—for example, to risk research, warning, and control-can be adapted to a common set of guidelines. Companies could use publicly stated levels of acceptable risk in their own risk management decisions. Without such clear guidance, manufacturers may be unwilling to produce socially beneficial but potentially risky products (e.g., vaccines) for fear of legal liability, should the courts decide in retrospect that the product was "unacceptably" risky.54 An explicit reliance on the portfolio approach avoids the "carcinogen of the month" problem because it leads the agency expressly to consider items to be placed on the lists without becoming either engulfed by them or too lax. Public scrutiny during rulemaking and judicial review under regulatory law will now work toward plausible solutions to difficult and polycentric problems.

Conclusions

The concept of "acceptable" risk levels seems easiest to justify as a device for constraining and guiding regulatory risk management efforts and resource allocation over time. It is less clearly applicable to the private decisions of economic agents (consumers or producers), where the availability of detailed case-specific information about costs, uncertainties, and benefits makes it reasonable to expect and require more careful and detailed approaches to case-by-case risk management.

Although the need for simple, concrete, easily implemented standards of acceptable risks for guiding private sector health and safety risk management decisions cannot be denied, it seems unlikely that this need can be met without ignoring some important aspects of risk and uncertainty. The acceptability of risks is not an easy question and generally may not have answers that are both easy to apply and fully defensible on rational or moral grounds.

In this paper, we have argued that the most realistic and constructive view of risk acceptability for the practitioner may be that it is a property of risk management decision processes, rather than of isolated risky activities or situations. Numerous cases in the recent history of risk litigation indicate that it is the interaction of such processes—as in the balancing of the proper role of judicial intervention against the expertise and discretion of regulatory agencies—that determines risk acceptability in particular cases. Acceptability of a technological risk is thus not only a matter of risk statistics and objective numbers, but of social processes and of trade-offs that society is willing to make to achieve decisions that are on average reasonably fair, efficient, workable, and acceptable.

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P. F. Ricci, L. A. Cox, "Acceptability of chronic health risks," Toxic Law Reporter 986 (1987).
 P. F. Ricci, L. S. Molton, "Health risk assessment: science, economics and law," Annual Review of Energy 11: 77 (1986).
 C. C. Travis, H. A. Hattemer-Frey, "Determining an acceptable level of risk," Environ. Sci. Technol. 22: 873 (1988).
 J. P. Dwyer, P. F. Ricci, "Coming to terms with acceptable risk," Environ. Sci. Technol. 23: 145 (1989).
 L. A. Cox, P. F. Ricci, "Risk, uncertainty and causation: quantifying human health risks," in The Risk Assessment of Environmental Hazards, D. J. Paustenbach, Ed., Wiley, New York, 1989, Chapter 2.

mental Hazaras, D. S. I adstendan, Ed., Whey, Item 1918, 1989, Chapter 2.
6. R. C. Elandt-Johnson, N. L. Johnson, Survival Models and Data Analysis, Wiley, New York, 1980.
7. S. D. Walter, "The estimation and interpretation of attributable risk in health research," Biometrics 32: 829 (1976).
7. A Cor "Ctatistical legislar in the estimation of estimated shares."

risk in health research," Biometrics 32: 829 (1976).

8. L. A. Cox, "Statistical issues in the estimation of assigned shares for carcinogenesis liability," Risk Analysis 7: 81 (1987).

9. F. A. Seiler, H. K. Scott, "Mixtures of toxic agents and attributable risk calculations," Risk Analysis 7: 61 (1987).

10. L. A. Cox, "Probability of causation and the attributable proportion of risk," Risk Analysis 4: 221 (1984).

11. L. A. Cox, "Comparative risk measures for heterogeneous populations," in Phenotypic Variation in Populations, A. Woodhead et al., eds., Plenum, New York, 1988.

12. D. Maclean, "Social values and the distribution of risk," in Values at Risk, D. Maclean, ed., Rowman and Allanheld, Totova, New Jersey, 1986.

Totowa, New Jersey, 1986.
13. P. C. Fishburn, P. D. Straffin, "Equity considerations in public risks evaluation," Operations Research 37: 229 (1989).
14. B. Fisschoff, S. Lichtenstein, R. Keeney, S. Derby, Acceptable Risk, Cambridge Univ. Press, London and New York, 1981.

15. R. L. Keeney, Siting Energy Facilities, Academic Press, New

K. L. Keeney, Stiing Energy ructimes, Readman, York, 1980.
 L. A. Cox, "Economic theory of compensation rule design for probabilistic injuries," in L. B. Lave, Ed., Risk Assessment and Management, Plenum Press, New York, 1987.
 William Aldred's Case, 77 Eng. Rep. 816 (1611).
 J. Trauberman, "Statutory reform of 'toxic torts': relieving legislations of the compensation on the chemical victim,"

gal, scientific, and economic burdens on the chemical victim,"

Harvard Environmental Law Review 7: 177 (1983).

19. O. F. Harris, "Toxic tort litigation and the causation element: is
there any hope of reconciliation?" Southwestern Law J. 40: 909

20. R. L. Rabin, "Environmental liability and the tort system," Houston Law Review 24: 27 (1987).
21. P. H. Schuck, "The new ideology of tort law," The Public Inter-

21. F. H. Schuck, The new ideology of tort law, The Public Interest 93 (Summer 1988).
22. Comment, "The inapplicability of traditional tort analysis to environmental risks: the example of toxic waste pollution victim compensation," Stanford Law Review 35: 575 (1983).
23. D. Rosenberg, "The causal connection in mass exposure cases: a 'public law' vision of the tort system," Harvard Law Review 97: 240 (1984).

849 (1984).
24. S. Gold, "Causation in toxic torts: burdens of proof, standards of persuasion, and statistical evidence," Yale Law J. 96: 376

25. T. A. Brennan, "Causal chains and statistical links: the role of scientific uncertainty in hazardous-substance litigation," Cornell Law Review 73: 469 (1988).

Sindell v. Abbott Laboratories, 26 Cal. 3d 588, cert. denied, 449 U.S. 912 (1980).

U.S. 912 (1980).
 P. H. Schuck, Agent Orange on Trial: Mass Toxic Disasters in the Courts, Harvard University Press, Cambridge, 1986.
 In re "Agent Orange" Product Liability Litigation, 597 F. Supp. 740 (E.D.N.Y. 1984).
 J. P. Dwyer, "Contentiousness and cooperation in environmental regulation," American Journal of Comparative Law 35: 809 (1987).

C. S. Diver, "Policymaking paradigms in administrative law," Harvard Law Review 95: 393 (1981).
 NRDC v. EPA, 824 F.2d 1146 (D.C. Cir. 1987).
 53 Fed. Reg. 28,496 (1988); 54 Fed. Reg. 9,914 (1989).
 N. A. Ashford, C. W. Ryan, C. C. Caldart, "Law and science of the control of the control

policy in federal regulation of formaldehyde," Science 222: 894

'34. Industrial Union Dep't, AFL-CIO v. American Petroleum In-

stitute, 448 U.S. 607, 615 (1980).

35. Id. at 628, 645

36. Chevron v. NRDC, 467 U.S. 837, 865-66 (1984).
37. J. R. Macey, "Promoting public-regarding legislation through statutory interpretation: an interest group model," Columbia Law Review 86: 223 (1986).
W. N. Eskridge, "Politics without romance: implications of pub-

lic choice theory for statutory interpretation," Virginia Law

Review 74: 275 (1988).
39. J. L. Mashaw, "Prodelegation: why administrators should make political decisions," Journal of Law, Economics and Organiza-

tion 1: 81 (1985).

40. C. S. Diver, "Statutory interpretation in the administrative state," University of Pennsylvania Law Review 133: 549 (1985).

41. 51 Fed. Reg. 28,331 (1986); 51 Fed. Reg. 28,346 (1986).

42. Alabama Power Co. v. Costle, 636 F.2d 323 (D.C. Cir. 1979).

43. 831 F.2d 1108 (D.C. Cir. 1987).

44. Ethyl Corp. v. EPA, 541 F.2d 1, 34-36 (D.C. Cir.), cert. denied, 426 U.S. 941 (1976).

426 U.S. 941 (1976).

45. EDF v. EPA, 465 F.2d 528, 537 (D.C. Cir. 1972).

46. 448 U.S. at 655-56.

47. 499 F.2d 467, 474-79 (D.C. Cir. 1974).

48. 838 F.2d 1258, 1264-67 (D.C. Cir. 1988).

49. Lead Industries Ass'n, Inc. v. EPA, 647 F.2d 1130 (D.C. Cir.), cert. denied, 449 U.S. 1042 (1980).

50. 727 F.2d 415 (5th Cir. 1984).

51. Baltimore Gas & Electric Co. v. NRDC, 462 U.S. 87, 103 (1983).

52. L. A. Cox, P. F. Ricci, "Legal and philosophical aspects of risk analysis," in The Risk Assessment of Environmental Hazards, D. J. Paustenbach, ed., Wiley, New York, 1989, Chapter 30.

53. S. Shavell, "A model of the optimal use of liability and safety regulation," Rand Journal of Economics 15: 271 (1984).

54. K. S. Abraham, R. A. Merrill, "Scientific uncertainty in the courts," Issues in Science and Technology 93 (Winter 1986).

courts," Issues in Science and Technology 93 (Winter 1986).

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Cancer Modeling

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Ideas in Pathology

Pivotal Role of Increased Cell Proliferation in Human Carcinogenesis

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Cancer develops secondary to multiple genetic events. Each time a cell divides there is a rare chance that a genetic error related to the carcinogenic process will occur. Thus, environmental agents or disease processes that produce sustained increased cell proliferation can enhance the likelihood of cancer development by providing additional cell divisions, each with an opportunity for spontaneous genetic error. Studies of hereditary cancers and of various DNA-damaging agents, such as radiation and certain viruses and chemicals, have provided insight into identification of the essential genes, but many examples of carcinogenesis in humans do not involve direct DNA damage. Also, most preneoplastic lesions in human carcinogenesis show increased proliferation compared with normal tissues, whether from increased mitotic rate, blocked differentiation, prolonged cell survival, or other mechanisms. Selected examples of proliferation-related carcinogenesis are described, including certain infectious agents, defective immune surveillance, hormonal imbalances, chronic inflammatory-regenerative processes, and exposure to various chemicals. A common biologic mechanism for these diverse stimuli is increased cell proliferation as a prelude to cancer. This mechanism seems essential to the genesis of many cancers in humans.

Key words: Cell proliferation, Carcinogenesis, Viral cancer, Chemical carcinogens, Genetics, Immune surveillance.

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Cancer, the second leading cause of death in the United States, may be increasing, particularly in elderly individuals (1). Although progress has been made in the treatment of patients with cancer, prevention offers greater opportunities for reducing the death toll. Cigarette smoking, responsible for a majority of cancers of the respiratory tract and cancers of other organs, remains the leading known

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cause of cancer (2). Specific chemicals known to be carcinogens in humans, such as 2-naphthylamine, benzidine, 4-aminobiphenyl, vinyl chloride, and diethylstilbesterol. account for only a small percentage of cancers (3). Infectious organisms have also been implicated as being etiologic agents of specific cancers (4), including enteric bacteria, parasites, such as Schistosoma and Clonorchis, and viruses, such as Epstein-Barr virus (EBV), human Tlymphotropic viruses I and II, hepatitis B virus (HBV), and human papilloma virus (HPV).

Mounting evidence strongly supports the contention developed in

1914 that cancer results from genetic alterations (5). Utilizing molecular biologic techniques, numerous genetic alterations, including specific genes, have been identified in several cancers. However, many etiologic agents do not directly cause genetic damage. Similarly, some environmental agents associated with cancers do not directly damage DNA. Thus, although genetic damage is most likely an eventual common pathway to the development of cancer, other pivotal mechanisms contribute to carcinogenesis.

That multiple events are essential for the development of cancer has been demonstrated in experimental animal models, in in vitro systems, and in certain human cancers. Nearly 50 years ago, Berenblum and Shubik [6) conducted classical experiments in mouse cutaneous carcinogenesis that resulted in the formulation of the two-stage carcinogenesis concept. Alfred Knudson (7) hypothesized that two genetic events occur for retinoblastomas to emerge in children. His hypothesis has been confirmed through numerous genetic analyses and ultimately by the molecular cloning of a specific Rb

Although cancer arises from defective control of cell proliferation, the etiologic and pathogenetic role of cell proliferation has received relatively little attention. Nevertheless, as early as 1953, Nordling (8) stated that, although genetic alterations were necessary, the likelihood that certain cancers would develop could be greatly augmented by sustaining cell prolifer-

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ation of the target tissue. A decade ago, a specifically define role for cell proliferation was integrated into a carcinogenesis model developed by Moolgavkar and coworkers (9, 10), which was derived from epidemiologic data, and into a biologically similar model formulated by Greenfield et al. (11) and by Cohen and Ellwein (12), using data from animal experiments. Although derived from two different perspectives, the biologic framework of both models is strikingly similar. They offer a basis for interpreting a wide variety of carcinogenesis data in animal models and humans. Both models quantify genetic and proliferative events and thus offer insight into assessments dealing with the risk of developing cancer. The framework of these models is presented below and then selectively illustrated in human carcinogenesis. We have attempted to identify the common biologic thread of increased cell proliferation as a common prelude to carcinogenesis. This perspective is not intended to be definitive and, thus, the important work of many investigators is not cited nor is the burgeoning information being published regarding multiple molecular events being discovered for specific histologic types of cancer.

CELL PROLIFERATION AND CARCINOGENESIS

The model of carcinogenesis discussed and illustrated herein is shown in Fig. 1. For any theoretic model, assumptions are made in defining qualitative and quantitative aspects. The assumptions of this model are the following: (a) cancer arises from normal cells through two irreversible genetic events; (b) these genetic events occur only during active cell proliferation or are irreversibly fixed only during cell division; (c) the carcinogenic events occur only in a susceptible subpopulation of cells within the target tissue (frequently referred to as stem cells); and (d)the two genetic events occur in a random fashion with non-zero spontaneous probabilities. Note that the word "transformation" is used to mean the development of malignant cells.

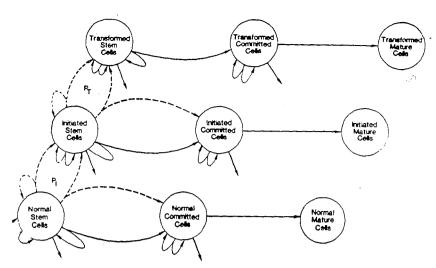


Figure 1. Diagrammatic representation of the biologic model of carcinogenesis originally described by Greenfield et al. (11). The bottom three circles represent the normal differentiation of a tissue. Ascending along the left side are the two stages of carcinogenesis, initiation and transformation. Downward-pointing arrows represent cell death, whereas the other arrows represent the various combinations of possible results of cells following cell division.

In the context of this model, an agent can alter the likelihood of developing a cancer in only two ways: it can increase the probability of irreversible genetic damage occurring during cell division; or it can increase cell proliferation, usually accompanied by an increase in cell number, and consequently increase the number of opportunities for spontaneous genetic damage. It also can do both. Although other models postulating more than two critical genetic events in the carcinogenic process have been proposed, our analyses reveal that two critical events seem to be sufficient for cancer to occur. We recognize that the size of the susceptible population of cells and their susceptibility can be altered by a variety of genetic and nongenetic events and stimuli. Also, further genetic alterations may occur in subclones of a malignancy, producing considerable heterogeneity with respect to several aspects of its biologic behavior. Clearly, other events occur during progression of cancers that endow the malignancies with increased survival advantage.

Under normal circumstances, the probability for either of the two critical genetic events to occur is exceedingly low (probably in the range of 10^{-10} to 10^{-6} per cell division); otherwise everyone would develop cancer at an early age. On the other hand, these probabilities are not zero, or no one would de-

velop cancer. Thus, this model predicts that, if people lived sufficiently long, all would develop cancer. However, because these probabilities are so low, the odds are in favor of an individual not developing cancer, even with a life span of 100 yr. Approximately 25% of persons develop malignancy in the United States during their lifetime.

INHERITED CANCERS

Studies of hereditary cancers of children have provided experiments of nature illuminating how carcinogenesis can occur. As originally advanced by Knudson (7), genetic events occur in the two alleles of the Rb gene that give rise to retinoblastoma (Fig. 2). Normally, the likelihood of developing retinoblastoma in an individual without an inherited retinoblastoma gene defect is rare, given that two rare events are required for the tumor. In contrast, individuals who inherit the defect in the Rb gene have nearly a 100% occurrence of the tumor. Although this phenotypic expression initially suggested a dominant trait, Knudson postulated autosomal recessive $R\bar{b}$ gene inheritance. With retinoblastic proliferation during development, a genetic error eventually occurs in the second Rb allele. Although rare during any one mitotic event, the probability that a mutation will occur is sufficiently high that nearly all genetically susceptible individuals develop retinoblastoma. Incidences frequently are bilateral, and/or persons develop more than one tumor per eye at an early age.

Retincblasts only proliferate during development of the eye, and cell division is necessary for either of the two genetic events in the genesis of retinoblastoma to occur (unless one allele is defective because of a germ line mutation). Thus, the chance of developing a retinoblastoma is eliminated once these cells stop proliferating. Similar arguments can be advanced for neuroblastoma, since neuroblasts also cease proliferating during childhood.

Knudson's hypothesis prompted the search for other tumor suppressor genes (also referred to as antioncogenes) (13, 14). Increased susceptibility to the development of tumors in other tissues, such as osteogenic sarcomas, has been observed in patients with retinoblastoma, although it remains unclear as to why tumors do not increase in all tissues. A second suppressor gene (with protein product p53) might be involved with the genesis of these sarcomas. Other possible candidates for tumor suppressor genes include Wilms' tumor, renal cell carcinoma, and at least two forms of inherited colonic carcinoma.

Polyposis coli (Pc) is an autosomal dominant, inherited susceptibility to adenomatous polyps and adenocarcinoma of the colon (15). Individuals with the Pc genetic defect (chromosome 5q) develop numerous colonic polyps that often evolve into carcinomas within a few decades. Similar genetic events occur in some nonpolyposis coli patients, who more commonly develop colon cancer at a later age. In addition, at least six other autosomal dominant hereditary traits predispose to colon cancer (16).

Adenomatous polyps, which are preneoplastic lesions, exhibit increased proliferative capacity, presumably due to enhanced proliferation of the colonic crypts. Most (if not all) preneoplastic lesions involved in human carcinogenesis show increased proliferation compared with normal tissue, whether

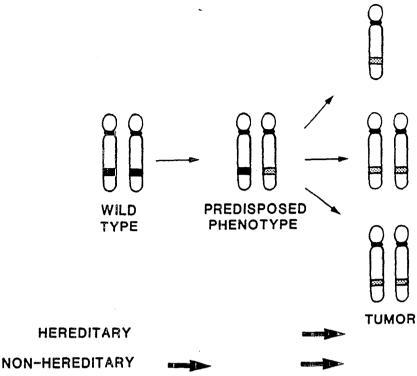
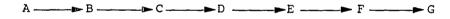


Figure 2. Genetics of retinoblastoma. Tumors occur when defects occur in both alleles, whether caused by absence of the entire chromosome, deletion of a portion or all of the gene segment, or mutation of the gene. Individuals with hereditary retinoblastoma are born with one defective allele in all of their cells, requiring only a defect to develop in the second allele for malignancy to occur. Nonhereditary individuals must generate defects in both alleles beginning with cells having two normal alleles at conception.



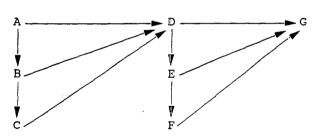


Figure 3. Alternative explanations of multiple genetic events occurring during carcinogenesis. If each of the identified genetic events occurs sequentially, the *upper diagram* pertains. However, more likely is a mechanism similar to that presented in the *lower diagram* where there are multiple genetic events that will affect the proliferative rates, genetic stability, and/or the cell population sizes of *A*, *B*, or *C*, but are not essential for the carcinogenic process itself. However, these additional genetic effects will greatly accelerate the carcinogenic process overall.

it comes from increased mitotic rate, blockage in differentiation, or other mechanisms.

Fearon and Vogelstein (17) have recently postulated a multistep process for colonic carcinoma. However, their multiple stage model could also be consistent with only two critical events being required for carcinogenesis (Fig. 3). The additional genetic alterations that they observe in other genes may enhance the proliferative capacity or alter the differentiation of cells in the preneoplastic, adenomatous polyp. Although these

secondary genetic alterations may give a proliferative advantage to preneoplastic cells, and may thus significantly decrease the time to the development of an actual malignancy, they nevertheless are not required, rate-limiting events in the development of the tumor.

HORMONES AND CANCER

Hormones govern numerous cellular functions, including proliferation, growth, and maintenance of bodily functions. Clinical and epidemiologic studies demonstrate that sustained hormonal stimulation (18) and consequent enhanced cell proliferation result in estrogendependent endometrial (19) and breast carcinomas (20), thyroid-stimulating hormone (TSH)-dependent thyroid tumors (21), and androgen and estrogen interactions in the development of prostatic cancer (22).

Endometrial carcinoma frequently results from chronic estrogen stimulation of cellular proliferation. For example, an increased incidence of endometrial adenocarcinomas results from exogenous estrogen therapy, such as seen with hormone replacement for menopausal women (19) and, possibly, from the use of older-type, estrogen-containing contraceptives (23). In addition, obesity is a risk factor for endometrial carcinoma, possibly due to hyperestrogenism from increased production or storage of estrogen by adipose cells (24). Moreover, chronic estrogen stimulation is associated with endometrial hyperplasia and carcinoma in women with the polycystic ovary syndrome (25). Characteristically, estrogen stimulates the endometrium to proliferate (Fig. 4). Normally, this proliferative stimulus is tempered in midcycle by the increased production of progesterone, ultimately resulting in the shedding of cells during menstruation. In the circumstances described above, estrogen stimulation is sustained rather than cyclic.

Estrogen-related substances, such as diethylstilbesterol (DES), stimulate estrogen-responsive cells. In experimental animals, DES induces a variety of estrogen-related tumors (26). In humans, the devel-

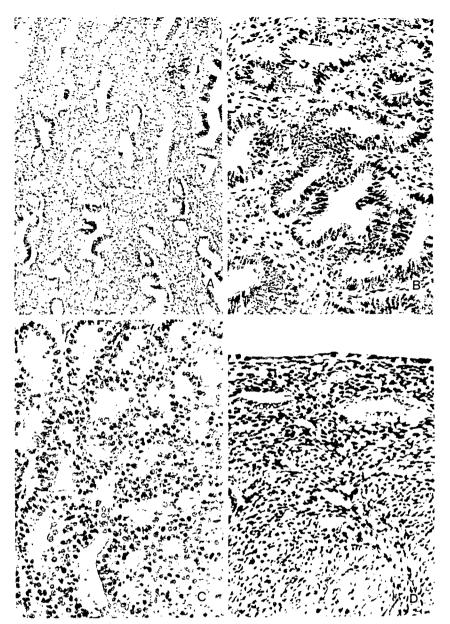


Figure 4. Estrogens have a proliferative effect on the endometrium. During the normal reproductive stage of a woman's life, this produces a proliferative endometrium (A), which is converted to secretory endometrium by progestational effects. However, if there is hyperestrogenism secondary to exogenous or endogenous sources, a hyperplastic endometrium results (B), since the proliferative effects of estrogen are not impeded by the normal or subnormal levels of progestins. If the adenomatous hyperplasia continues, a malignant tumor, adenocarcinoma, arises (C). This is particularly striking in postmenopausal women who have hyperestrogenism secondary to exogenous sources, but also can occur secondary to endogenous production. In contrast, postmenopausal women usually have lost the proliferative-stimulatory effects of estrogen, and their endometrium becomes atrophic (D).

opment of vaginal adenocarcinomas in the offspring of mothers who were exposed to DES during pregnancy is a notorious example (27). DES given to experimental animals, particularly in the hamster kidney model, undergoes metabolic activation and DNA adduct formation (28). However, the principal role of DES in tumorigenesis

appears not to involve DNA adduct formation but increased cell proliferation of estrogen-responsive cells (29). The situation in the human may reflect both of these components. The initial event in utero is likely due to interaction of DES with the DNA of specific vaginal cells. These initiated cells undergo rapid cell proliferation following

menarache, often leading to the carcinogenic second event.

The role of estrogen, and possibly other hormones, in causing breast cancer is similar to that in the endometrium (20). However, other critical factors may affect the responsiveness of cells to estrogen stimulation. For example, the age at which a woman has her first child significantly influences her susceptibility to breast cancer: the younger the woman is at the time of her initial pregnancy, the less likely she is to develop breast cancer. During pregnancy, terminal differentiation of the breast ductules occurs, removing a large number of cells from the cancer-susceptible population. Thus, even if these cells are subsequently stimulated to increased proliferation, they are not susceptible to developing cancer. Human chorionic gonadotropin (HCG) also appears to be involved with the induction of this differentiation process. An initial pregnancy at a later age prolongs the susceptible period of these cells. Not only is the rate of cell proliferation important, but the size of the susceptible cell population and the period of time over which it persists influence the chances for experiencing the critical events necessary for developing cancer.

Chronic increased cell proliferation induced by estrogen also increases the appearance of benign and malignant hepatocellular tumors in experimental animals and in humans (30). Hepatocytes with estrogen receptors respond to increased estrogen levels by dividing more frequently.

Hormonal effects on cell proliferation also greatly affect the likelihood of developing prostatic adenocarcinoma (22). Animal models have been developed wherein the prostate is provoked into a burst of cell proliferation. This proliferation can then be hormonally sustained, leading to the development of adenocarcinomas. In these instances, it remains unclear what the interactions between androgens and estrogens are, but both and possibly other hormones appear to be involved.

Thyroid carcinogenesis involves the interaction between the thyroid and the pituitary in a feedback loop

(18, 21). As the thyroid produces more thyroid hormone $(T_3 \text{ or } T_4)$, it inhibits the pituitary, reducing TSH production. If thyroid hormone levels decrease, TSH levels produced by the pituitary increase. resulting in increased thyroid proliferation. In animal models, this process is frequently seen following the administration of chemicals (21) that decrease levels of thyroid hormone by a variety of mechanisms. This ablates negative feedback on the pituitary and, consequently, overproduction of TSH results and thyroid follicular cell proliferation arises. Ultimately, thyroid tumors result. Again, there is no evidence that TSH damages DNA by itself; these tumors arise as a consequence of chronic increased cell proliferation of the target tissue. This mechanism is nongenotoxic, but a thyrotoxic chemical can ultimately evoke tumors in the target organ.

INFECTIOUS ORGANISMS AND CANCER

Several microbial agents increase cell proliferation and increase the risk of developing cancer. The intriguing possibility that infectious organisms might cause cancer has been investigated for more than a century. The first transmissible carcinogenic viral agents were identified in experiments by Rous and by Ellerman and Bang during the early part of this century (31). Cell-free extracts were found to transmit cancer from diseased to disease-free animals.

Some fungi have been implicated in cancer development by producing specific carcinogenic toxins, for example, aflatoxin (32). Bacteria have also been associated with the production of carcinogenic chemicals. For example, enteric bacteria occasionally are involved in the metabolic activation of certain carcinogens, such as cycasin (33). Other organisms more directly cause specific cancers.

Immunoproliferative small intestinal disease (IPSID) is found in males in Third World countries. The initial benign appearing hyperplastic lymphoid lesion is thought to arise from chronic antigenic stimulation by bacterial li-

popolysaccharides or enterotoxins of Vibrio cholerae. Supporting this view is the regression of the lesions following a 6-mo trial of tetracycline (34). Without treatment, these lesions can convert to monoclonal malignant lymphoma that secretes α heavy chains of immunoglobulin.

Certain parasitic diseases increase susceptibility to cancer most notably schistosomiasis (35) and clonorchiasis (36). Chronic Schistosoma hematobium infection is associated with a markedly increased risk of developing bladder cancer. This agent causes chronic inflammation, fibrosis, squamous metaplasia, and sustained, increased, squamous cell proliferation compared with the normal, mitotically quiescent transitional epithelium (Fig. 5). The majority of the tumors that develop within these infected bladders are squamous cell carcinomas, rather than the usual transitional cell carcinomas. Although specific carcinogens, such as nitrosamines, may be produced in schistosomiasis, sustained increased cell proliferation is pivotal to generating these tumors.

Schistosomal infections of the lower gastrointestinal tract (S. mansoni and S. japonicum), common in the Far East and elsewhere, are associated with development of colonic carcinomas (37). This association is considerably less frequent than with schistosomiasis and bladder cancer. Again, sustained increased proliferation of the colonic epithelium may be a mechanism responsible for these cancers.

Chronic biliary tract infections with the flukes, Clonorchis sinensis (36) or Opisthorchis viverrini (38), evoke destruction, epithelial regeneration, and an increased prevalence of cholangiocarcinoma (Fig. 6). A specific carcinogen is not implicated in this process, whereas increased cell proliferation is sustained in bile ducts and ductules.

Although on a worldwide basis these infections and tumors are common, they seldom affect persons in economically developed countries. In contrast, specific RNA and DNA viruses infecting populations globally can be carcinogenic (31, 39).

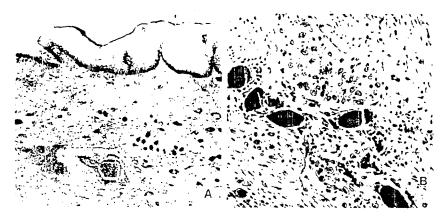


Figure 5. Squamous cell metaplasia (A) of the urinary bladder in a patient with chronic schistosomiasis. There is also ulceration of the epithelium. Note the numerous schistosome organisms in the wall of the bladder. The organisms can also be seen in the poorly differentiated squamous cell carcinoma that arose in another patient with schistosomiasis (B).

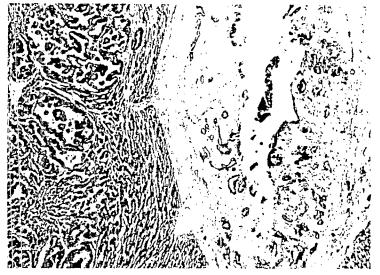


Figure 6. Bile ductular proliferation (right) secondary to *Clonorchis* infection, which has given rise to a cholangiocarcinoma (left).

Numerous oncogenic RNA retroviruses affect animals. Retroviruses convert viral RNA to DNA by utilizing the reverse transcriptase enzyme; the DNA is then incorporated into the genome of the host. It has been hypothesized that specific viral oncogenes have been incorporated into the human genome as protooncogenes or cellular oncogenes (39, 40). These viral and human cellular homologs act in a genetically dominant fashion. The Rous sarcoma virus carries the viral src gene. Several other viral oncogenes of retroviruses that infect humans have been identified and can result in leukemia or lymphoma.

Other retroviruses can produce cancers without carrying a specific

oncogene as part of their RNA (39, 40) by increasing the proliferation of the target tissue. Transmission of virus occurs from cell to cell, eventually resulting in the interposition of virally generated DNA next to a cellular oncogene. Thus, sustained cell proliferation and, ultimately, tumors can arise. A single oncogene, such as bcl-2 involved in follicular lymphoma, appears incapable of producing cancer without a second event. This oncogene, which is activated by the reciprocal translocation t(14;18) involving the breakpoint at bcl-2 on chromosome 18 and the heavy chain locus at 14q32, enhances follicular center cell proliferation. A second event is needed for the malignant counterpart to emerge.

The human oncogenic retrovirus, human T-cell leukemia virus (HTLV) I, chronically infects nearly 1 million people in Japan. Given that only 400 patients develop adult T-cell leukemias yearly in Japan, it is evident that a multistep process prevails. It has been postulated that immune deficiency and genetic events are involved in this leukemogenicity (41).

Infection with human immunodeficiency virus (HIV) results in an increased susceptibility to malignant lymphomas, squamous cell carcinomas, and Kaposi's sarcoma, but does not seem to be directly oncogenic (42) (see below under "Immune Surveillance of Cancer").

Several DNA viruses, including hepatitis B virus (HBV), human papilloma virus (HPV), and Epstein-Barr virus (EBV), are associated with certain types of cancers in humans. In each instance, the development of the malignancies results from a sustained proliferation of the target cell. Herpes viruses I and II have also been associated with an increased risk of cervical cancer, although this association has not been confirmed by recent research (43).

HBV infection is mostly asymptomatic and transient. However, in susceptible individuals, the acute infection leads to sequelae of chronic active hepatitis (Fig. 7). which can progress to cirrhosis (44). Likely, the virus persists predominantly in males owing to an inadequate immune response to the virus. The male:female ratio of primary hepatomas is 4:1. Females have superior immunocompetence to HBV than do males, as has been shown in studies done in Taiwan (45). Increased androgens may also enhance hepatocarcinogenesis.

The characteristic features of chronic active hepatitis and cirrhosis are hepatocellular necrosis simultaneously with regenerative repair. The normal liver is a mitotically quiescent tissue as is the urinary bladder epithelium. With chronic active hepatitis or cirrhosis, hepatocyte proliferation is markedly increased and is sustained for the life of the patient. In a significant number of such patients, hepatoma arises. Worldwide, hepatomas are caused primarily by chronic HBV (46).

HBV-related hepatocarcinogenesis is probably not related directly to a specific oncogenic DNA alteration induced by the virus itself. Transgenic mice that overproduce the large envelope polypeptide of HBV accumulate hepatitis B surface antigen and develop chronic active hepatitis, regenerative nodules, and ultimately hepatomas (47). This protein has none of the characteristics of oncogenes or tumor suppressor genes, but rather appears to be involved with the development of hepatocellular necrosis, chronic active hepatitis, and sustained, increased hepatocyte proliferation.

Any situation resulting in a chronic inflammatory or cirrhotic

process is associated with an increased proliferative rate, regenerative nodules, and an increased risk of hepatomas. Examples include chronic alcoholism and a variety of hereditary disorders, such as hemochromatosis. Not one of these conditions causes specific genetic damage, but they have in common increased sustained cell proliferation.

HPV infects squamous epithelia and is most commonly associated with cervical squamous cell carcinoma. Also, squamous cell carcinomas of the penis, skin, anus, and oral cavity frequently contain the virus (48). HPV blocks differentiation of the infected epithelium, giving features of dysplasia (Fig. 8).

Increased cell proliferation and expansion of the basal cell compartment result. Since HPV infections are usually persistent, events leading to the continued presence of dysplasia can evolve, occasionally leading to carcinoma in situ and squamous cell carcinoma (49). Again, HPV causes a greatly increased risk of carcinoma owing to enhanced cell proliferation. Smoking cigarettes and defective immune responsiveness to the virus also appear to play a role (48, 50).

EBV is a well-known B-cell mitogen. The virus infects B-cells through the C3d (CR2) receptor and immortalizes them in vitro. During acute infectious mononucleosis (Fig. 9), approximately one per 104 B-cells is infected, whereas during latency approximately one per 106 B-cells is infected. Multiple immune responses, especially by Tcells, bring the B-cell proliferation under control (51). However, if the polyclonal B-cell proliferation is not brought under control, Burkitt's or other non-Hodgkin's lymphomas can arise. Immune-deficient individuals chronically immunosuppressed by holoendemic malaria, children with inherited immunodeficiency, HIV-infected persons, or transplant recipients frequently develop EBV-carrying tumors.

Klein and Klein (52) postulated a multistep scenario in the genesis of African Burkitt's lymphoma. Holoendemic malaria suppresses cytotoxic T-cells against EBV-infected B-cells while simultaneously causing polyclonal B-cell prolifer-

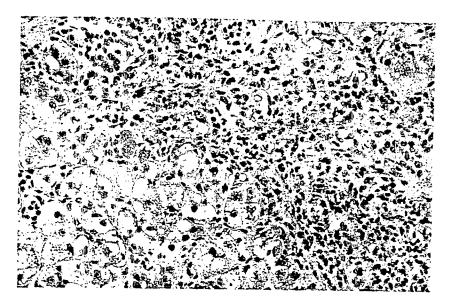
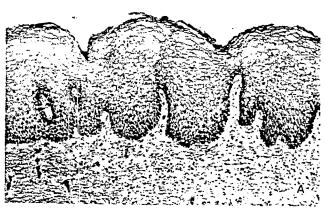


Figure 7. Chronic active hepatitis secondary to HBV infection. This is a chronic necroinflammatory process with sustained regeneration, occasionally leading to the development of hepatoma.



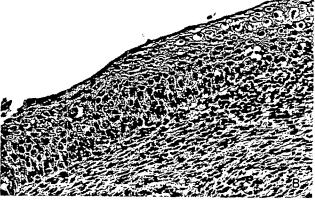


Figure 8. The normal squamous epithelium of the cervix shows a "stem cell" basal layer with differentiation progressing to the surface (A). With HPV infection, there is blockage of this differentiation process leading to an expansion of the proliferative pool of cells extending higher in the epithelium, above the basal layer (B). In this figure, there is clear evidence of HPV infection as indicated by the koilocytes and chronic inflammation, with increasing degrees of dysplasia progressing from right to left.

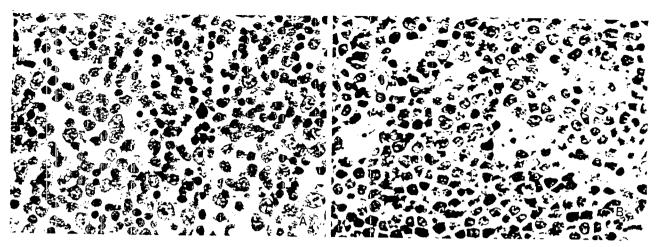


Figure 9. Infectious mononucleosis (A) is a markedly proliferative acute infection secondary to EBV, which is normally brought under control by various immune factors. In immunosuppressed patients, this control of B-cell proliferation does not occur. The sustained proliferation can eventuate in the development of B-cell lymphomas, such as Burkitt's lymphoma (B).

ation. This increased cell proliferation increases the random chance that a specific chromosomal translocation might occur involving the c-myc protooncogene at 8q24 with corresponding breakpoints involving immunoglobulin loci (14q32, 2p12, or 22q11). Juxtaposition of an Ig gene with c-myc promotes expression of the c-myc gene product. Concurrently, the major histocompatibility complex (MHC) and EBV viral targets for T-cell surveillance are down regulated. Identical chromosomal translocations are seen in mouse and rat immunocytomas and plasmacytomas. Moreover, the Ig-myc transgene results in transgenic mice that develop pre-B-cell malignant lymphomas (53).

In cell culture systems, EBV readily produces a mitogenic response in B-cells but does not result in the production of malignant transformation (54). This suggests that EBV does not have a specific malignant transforming gene and that the specific chromosomal translocation leading to Burkitt's lymphoma is an exceedingly rare event. The probability that any particular cell division will produce a malignant transformation is not increased, but, in the patient wherein uncontrolled polyclonal Bcell proliferation persists, the number of cell divisions is enormously increased. The odds of a chromosomal translocation occurring within the susceptible pre-B-cell population are thus increased.

IMMUNE SURVEILLANCE OF CANCER

In 1957, Burnet proposed the notion that the immune system routinely recognizes and eliminates newly generated cancer cells. This hypothesis was extended Thomas in 1959 (see Ref. 55). Cancer was proposed to arise chiefly because of a breakdown in the immune surveillance against cancer cells. This theory was based on several experimental observations. In mice, tumor-specific antigens were identified, suggesting that tumor cells had specific antigens that could be detected by the immune system and eliminated. Furthermore, several viral and chemical carcinogens were demonstrated to have immunosuppressive properties in animal models. Further, supporting this theory, clinical observations indicated that patients with congenital immunodeficiencies, such as Wiskott-Aldrich syndrome, or acquired immunodeficiency secondary to immunosuppressive therapy for renal transplantation had a markedly increased occurrence of malignancies.

Although superficially plausible, additional observations and experimentation have revealed that the immune surveillance theory of carcinogenesis is not correct. The tumor-specific antigens that were discovered in mice were determined to be related primarily to tumorigenic viruses or H-2 antigens. Tu-

mor-specific antigens in human cancers have only been discovered in multiple myeloma (56). A wide variety of tumor-associated antigens have been identified, which are embryonic or differentiation antigens of normal cells. Although qualitative differences have not been identified, quantitative differences between normal cells and cancer cells have been demonstrated.

The immunosuppressive effects of a variety of carcinogens, particularly the polycyclic aromatic hydrocarbons, and some of the carcinogenic viruses are immunosuppressive only at doses far in excess of those known to cause cancer, or they are immunosuppressive using routes of administration unrelated to the carcinogenicity studies (57). For other chemicals or viruses shown to be carcinogenic in various animals, immunosuppressive properties could not be demonstrated. Also, many experimental models were shown to be unaffected when immunosuppressants, such as azathioprine or cyclophosphamide, were administered concurrently or sequentially with the carcinogenic agent (58).

Although a marked increased prevalence of malignancies occurs in immunocompromised patients (59), all types of malignancies are not increased; only B-cell lymphomas, Kaposi's sarcoma, and cutaneous, oral, anal, and uterine cervical squamous cell carcinomas (Fig. 10) are increased (59, 60). As

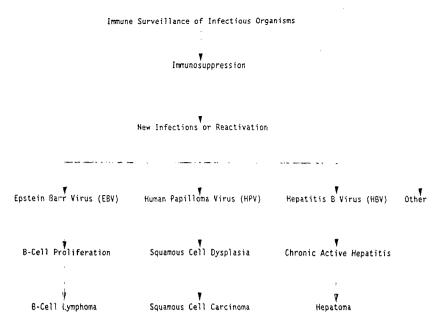


Figure 10. Diagrammatic representation of the role of immune surveillance of various infectious organisms in the etiology of specific cancers. The immune system normally controls the acute infection. If the patient is immunosuppressed (hereditary, transplantation, AIDS), chronic proliferative effects ensue from the uncontrolled infections, occasionally resulting in malignancy.

described above, these malignancies have been associated with viruses. EBV is present in the B-cell malignancies and HPV in the squamous cell carcinomas. Kaposi's sarcoma occurs in AIDS patients, possibly arising from the Tat gene of HIV or growth factors liberated by stimulated T-cells, or other, yet to be identified, factors (61). The common biologic theme among these tumors is a chronic increased proliferation of the target cells resulting from persistent, new, or reactivated viral infections. Immunity controls the extent of production and persistence of these viruses.

Thus, immune surveillance is germane to carcinogenesis with these specific, virus-induced tumors. Surveillance, however, is not against malignant cells but against the infectious organisms. As indicated above, excellent examples of this are the EBV-induced lymphoid malignancies in immunosuppressed patients that result from a failure of T-cells to recognize Epstein-Barr viral antigens on the surface of infected B-cells and to eliminate them. The sustained cell proliferation leads to a substantially increased risk of cancer.

Although there is little evidence to support the immune surveillance theory of carcinogenesis as originally described in the 1950s and 1960s, immune surveillance is plausible for microbe-induced cancers that act primarily through producing mitogenesis. The immune system under Darwinian evolutionary pressures evolved to protect the host against life-threatening infections and not cancer. Malignancies occur largely during the postreproductive period and, thus, natural selection would not occur. However, immunologic regulation of the invasiveness and metastatic potential of cancers, such as melanomas, bladder carcinomas, leukemia, lymphoma, and renal cell carcinomas, may be important (62).

CHRONIC INFLAMMATORY PROCESSES

As summarized above, many chronic inflammatory processes increase the risk that cancer might develop. In addition, in the gastrointestinal tract, notable examples are the association of chronic atrophic gastritis with gastric carcinoma (63) and chronic ulcerative colitis with colonic carcinoma (64). A chronic necroinflammatory process results in sustained regenerative proliferation of cells that gain a proliferative, and possibly a sur-

vival, advantage greater than the surrounding normal tissue. Gastric intestinal metaplasia or colonic epithelial dysplasia ensues that can develop into proliferative foci, adenomatous polyps, and adenocarcinomas.

The presence of agents that enhance the proliferative process, such as high salt intake or *Helicobacter* infections associated with the stomach (63, 65), or bile acids, high fat, and low fiber diets with the colon (66), predisposes to development of cancer. Conversely, dietary calcium, high fiber, and low fat are associated with decreasing colonic cancer risk by decreasing proliferation (66, 67).

Gallstones and gallbladder and biliary tract cancer (68), tropical phagedenic ulcer and squamous cell carcinoma of the skin (69), and chronic esophagitis secondary to gastric reflux leading to Barrett's esophagus and adenocarcinoma (70) are other situations characterized by sustained cellular proliferation and frequent carcinogenesis (Table 1).

In a similar vein, high rates of growth of normal tissues are also associated with an increased risk of cancer. For example, osteogenic sarcoma incidence peaks during adolescence when growth is marked (71). Osteogenic sarcomas in older individuals are frequently associated with Paget's disease, a disease associated with an increased proliferative process of the osteoblasts (72).

CELL PROLIFERATION AND CHEMICAL CARCINOGENS

Numerous chemicals and chemical mixtures increase the risk of developing cancer, including cigarette smoking, snuff use, betel quid chewing, aromatic amines, polycyclic aromatic hydrocarbons, nitrosamines, and others as detailed in a recent IARC monograph (26). Most of these chemicals are both mutagenic in short-term screening assays and carcinogenic in a variety of species. They are also cytotoxic to the target tissue, resulting in regeneration and increased cell proliferation (Fig. 11). At toxic doses, a sharp increase in the rate of tumor formation is observed.

TABLE 1. SOME OF THE CHRONIC CONDITIONS ASSOCIATED WITH INCREASED CELL
PROLIFERATION AND INCREASED RISK OF CANCER DEVELOPMENT

| Organ | Chronic Condition |
|-------------|---|
| Skin | Phagedenic ulcer |
| Esophagus | Reflux esophagitis with Barrett's esophagus |
| Stomach | Chronic atrophic gastritis |
| Colon | Chronic ulcerative colitis |
| Liver | Cirrhosis |
| Gallbladder | Cholelithiasis |
| Bone | Paget's disease |

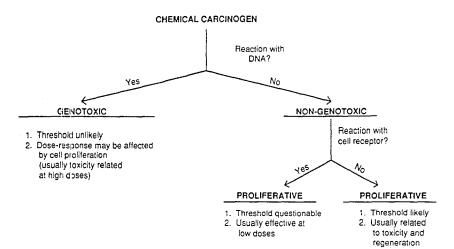


Figure 11. Diagrammatic representation of proposed classification of chemical carcinogens based on their ability to react directly with DNA or cell receptors. Cell proliferation affects the dose-response of all classes of chemical carcinogens [From Cohen and Ellwein (12)].

Similarly, UV radiation is associated with skin carcinomas (73); high energy radiation with cancers of the bone marrow (leukemia), thyroid, breast, and other tissues (73); and thorotrast with liver and kidney cancers (74). These forms of radiation are obviously genotoxic, but the development of tumors secondary to radiation is frequently associated with chronic, destructive-regenerative processes.

Although the carcinogenic synergism associated with the proliferative effects of chemicals has been best documented in experimental animals, this likely holds for humans also. For example, cigarette smoke is toxic to the respiratory epithelium, leading to chronic bronchitis and squamous metaplasia, associated with increased cell proliferation (75). In addition, cigarette smoking produces hyperplasia and carcinoma of the urinary bladder (76). Snuff and other orally used tobacco products contain many carcinogens, but they are also associated with

chronic inflammatory, regenerative processes in the oral cavity and pharynx (77). Likely, the combination of their genotoxicity and increased cell proliferation results in cancer in these tissues in humans.

When tested in experimental bioassays for carcinogenic activity, a large proportion of chemicals that are negative in various short-term mutagenicity screens show carcinogenic activity in mice and/or rats (78). This raises concern regarding the interpretation of these data and the extrapolation of potential risk to humans for compounds in the environment or food supply. A major complication in assessing risk from these chemicals is that tumors usually occur only at high, often toxic, doses that are frequently associated with increased cell proliferation of the target tissue (12).

For nongenotoxic chemicals that demonstrate proliferative effects only at very high doses, a no-effect threshold might exist (12). For example, when melamine is administered to rats or mice at high doses, urinary calculi form, and ultimately, bladder tumors develop (12, 79, 80). When lower doses of melamine are administered and calculi do not form, cell proliferation is not increased and no tumors form. The data regarding melamine and related compounds that induce calculi in experimental animals only at high doses imply that there is no carcinogenic risk for humans exposed at low doses, where calculi do not form. The Environmental Protection Agency (EPA) has recently followed this pragmatic logic and an understanding of biologic mechanisms in interpretating data for melamine (81).

Another example with a similar mechanistic action is sodium saccharin. It induces bladder cancer only in rats, particularly in males, but not in mice, hamsters, or monkeys (12, 82). The tumorigenic effect of sodium saccharin is likely due to formation of silicates in the urine of male rats. Factors, including pH, protein, sodium, silicate, and saccharin, reach critical levels in the urine following feeding of high doses of sodium saccharin to rats. A threshold effect is likely. If lower doses of sodium saccharin are administered, silicate precipitates and crystals do not form, cell proliferation is not increased, and there is no increased tumor formation. Moreover, the critical set of urinary parameters in the rat following high doses of sodium saccharin is not present in humans, mice, or monkeys. Hence, humans appear to be resistant and would not be expected to develop bladder cancer even at extremely high doses of sodium saccharin.

Assessment of risk of chemical compounds is controversial. Regulatory agencies are determining whether differences should be made in interpreting data between nongenotoxic and genotoxic compounds. Genotoxic compounds generally do not appear to have a threshold regarding their genotoxic effects, but the tumorigenic response is greatly augmented at doses producing increased cell proliferation. In contrast, most (if not nongenotoxic compounds likely require a threshold dose for increasing cell proliferation, and consequently, they are likely to

have a no-effect threshold with respect to tumorigenesis. This is particularly true for nongenotoxic chemicals that act through a mechanism not directly involving a cell receptor.

Substantial difficulties arise in interpreting the carcinogenic potential of many chemicals, exemplified by asbestos (83). For example, controversy continues as to whether asbestos itself is genotoxic, since it has clastogenic activity in some cell culture systems. Also of significance, exposure of limited duration to asbestos is actually lifetime exposure, since it remains within the mesothelial cells. Thus, it provides a chronic proliferative stimulus even if the actual environmental exposure was relatively brief. The challenge remains to ascertain whether there is a minimal lével of chronic proliferation that determines whether there is a no-effect threshold exposure level with respect to asbestos-induced carcinogenesis in humans.

CONCLUSIONS

We have presented a two-event model of carcinogenesis, wherein agents increase the likelihood of developing cancer by increasing the probability of genetic damage during each cell mitosis or by increasing the number of cell divisions subject to spontaneous genetic damage probabilities (i.e., cell proliferation), or by doing both. Whether cancer occurs by two, or more, critical genetic events, these two general mechanisms remain as the only ones by which an agent can increase cancer risk. Agents causing direct genetic damage during cell division, such as radiation and genotoxic chemicals, are not likely to have a threshold for carcinogenic response. Further, the dose-response can be significantly influenced by the cytoxicity and regenerative hyperplasia that follow exposure to these agents at high doses.

For agents that act only by increasing cell proliferation, whether nongenotoxic chemicals, infectious organisms, or chronic inflammatory processes, the magnitude and duration of the increased proliferative processes are integral to car-

cinogenesis. Brief responses will probably not be associated with a detectable increased risk of cancer, since any increased proliferation will be of short duration and contribute little to the total number of cell divisions during which spontaneous genetic damage might occur.

Both genetic damage and increased cell proliferation act in human and in animal carcinogenesis. Study of the complex of biochemical and physiologic adaptive and maladaptive tissue processes offers numerous opportunities for enhancing our understanding of the carcinogenic process and for designing preventive intervention strategies.

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REFERENCES

- Cancer Facts and Figures. New York, American Cancer Society, 1989.
 Loeb LA, Ernster VL, Warner KE, Abbotts J,
- Loeb LA, Ernster VL, Warner RE, Abbotts J, Laszio J: Smoking and lung cancer: an overview. Cancer Res 44:5940, 1984
- Tomatis L, Aitio A, Wilbourn J, Shuker L: Human carcinogens so far identified. Jpn J Cancer Res 80:795, 1989
- Rubin E, Farber JL: Neoplasia. In Pathology, edited by Rubin E, Farber JL. Philadelphia, JB Lippincott Company, 1988
- Boveri T: Zur Trage der Entstehung maligner Tumoren, edited by Jena, Fischer, 1914
- Tumoren, edited by Jena, Fischer, 1914
 6. Berenblum I, Shubik P: A new quantitative approach to the study of the stages of chemical carcinogenesis in the mouse's skin. Br J Cancer 1:383, 1947
- Knudson AG: Mutation and cancer: statistical study of retinoblastoma. Proc Natl Acad Sci USA 68:820, 1971
- Nordling CO: A new theory on the cancerinducing mechanism. Br J Cancer 7:68, 1953
- Moolgavkar SH, Knudson AG Jr: Mutation and cancer: a model for human carcinogenesis. JNCI 66:1037, 1981
- 10. Moolgavkar SH, Luebeck G, deGunst M: Two

- mutation model for carcinogenesis: relative roles of somatic mutations and cell proliferation in determining risk. In Scientific Issues in Quantitative Risk Assessment, edited by Moolgavkar SH, p 136. Boston, Birkhäuser, 1990
- Greenfield RE, Ellwein LB, Cohen SM: A general probabilistic model of carcinogenesis: analysis of experimental urinary bladder cancer. Carcinogenesis 5:437, 1984
- Cohen SM, Ellwein LB: Cell proliferation in carcinogenesis. Science 249:1007, 1990
- Knudson AG Jr: Two-event carcinogenesis: roles of oncogenes and antioncogenes. In Scientific Issues in Quantitative Risk Assessment, edited by Moolgavkar SH, p 32. Boston, Birkhäuser, 1990
- Sager R: Tumor suppressor genes: the puzzle and the promise. Science 246:1406, 1989
- Knudson AG Jr: Hereditary cancers: clues to mechanisms of carcinogenesis. Br J Cancer 59:661, 1989
- Purtilo DT, Pacquin LA, Gindhart T: Genetics of neoplasia: impact of ecogenetics on oncogenesis. Am J Pathol 91:609, 1978
- Fearon ER, Vogelstein B: A genetic model for colorectal tumorigenesis. Cell 61:759, 1990
- Furth J: Conditioned and autonomous neoplasms; a review, Cancer Res 13:477, 1953
- Ziel HK, Finkle WD: Increased risk of endometrial carcinoma among users of conjugated estrogens. N Engl J Med 293:1167, 1975
- Russo J, Gusterson BA, Rogers AE, Russo IH, Wellings SR, van Zwieten M: Biology of disease: comparative study of human and rat mammary tumorigenesis. Lab Invest 62:244, 1990
- Hill RN, Erdreich LS, Paynter OE, Roberts PA, Rosenthal SL, Wilkinson CF: Thyroid follicular cell carcinogenesis. Fundam Appl Toxicol 12:697, 1989
- Bosland MC: The etiopathogenesis of prostatic cancer with special reference to environmental factors. Adv Cancer Res 51:1, 1988
- Key TJA, Pike MC: The dose-effect relationship between "unopposed" oestrogens and endometrial mitotic rate: its central role in explaining and predicting endometrial cancer risk. Br J Cancer 57:205, 1988
- Bolt HM, Gobel P: Formation of estrogens from androgens by human subcutaneous adipose tissue in vitro. Horm Metab Res 4:312, 1976
- Coulam CB, Annegers JF, Kranz JS: Chronic anovulation syndrome and associated neoplasia. Obstet Gynecol 61:403, 1983
- Some naturally occurring substances. IARC Monogr Eval Carcinog Risk Chem Man 10:153, 1975
- 27. Herbst AL. The effects in the human of diethylstilbestrol (DES) use during pregnancy. In Proceedings of the 18th International Symposium of the Princess Takamatsu Cancer Research Fund, p 67. Tokyo, Japan Scientific Societies Press, 1988
- Liehr JG, Randerath K, Randerath E: Target organ-specific covalent DNA damage preceding diethylstilbesterol-induced carcinogenesis. Carcinogenesis 6:1067, 1985
- Henderson BE, Ross RK, Pike MC, Casagrande JT: Endogenous hormones as a major factor in human cancer. Cancer Res 42:3232, 1992
- Barrows GH, Mays ET, Christopherson WM: Steroid related neoplasia in human liver. In Proceedings of the 18th International Symposium of the Princess Takamatsu Cancer Research Fund, p 47. Tokyo, Japan Scientific Societies Press, 1988
- Pimental E: Oncogenes. Boca Raton, FL, CRC Press, 1986
- Miller EC, Miller JA: Carcinogens and mutagens that may occur in foods. Cancer 58:1795, 1986
- Hirono I: Natural carcinogeneic products of plant origin. Crit Rev Toxicol 8:235, 2981
- 34. Khojasteh A, Haghighi P: Immunoprolifera-

- 35. El-Bolkainy MN: Schistosomiasis and bladder cancer. In The Pathology of Bladder Cancer, edited by Bryan GT, Cohen SM, Vol I, p 57. Boca Raton, FL, CRC Press, 1983 36. Purtilo DT: Clonorchiasis and hepatic neo-
- plasms. Trop Geogr Med 28:21, 1976
- 37. Gutierrez Y: The trematodes of blood vessels: the schistosomes-schistosomiasis. In Diagnostic Pathology of Parasite Infections with Clinical Correlations, p 393. Philadelphia, Lea and Febiger, 1990
- 38. Kurathong S, Lerdverasirikul P, Wongpaitoon V, Pramoolsinsap C, Kanjanapitak A, Varavithya W, Phuapradit P, Bunyaratvej S, Upatham ES, Brockelman WY: Opisthorchis viverrini infection and cholangiocarcinoma. Gastroenterology 89:151, 1985
- 39. Varmus H: Retroviruses. Science 10:1427. 1988
- 40. Tomasi TB: Retroviruses, oncogenes, and cancer. Adv Pathol 1:229, 1988
- 41. Purtilo DT: Lymphotropic viruses, Epstein-Bair virus (EBV), and human T-lymphotropic virus-I (HTLV-I), adult T-cell leukemia virus (ATLV), and HTLV-III/human immune deficiency virus (HIV) as etiological agents of malignant lymphoma and immune deficiency. AIDS Res 2:S177, 1986
- 42. Purtilo DT, Manolov G, Manolova Y, Harada S, Grierson H: Squamous cell carcinoma, Kaposi's sarcoma, and Burkitt's lymphoma are consequences of impaired immune surveillance of ubiquitous viruses in acquired immune deficiency syndrome, allograft recipients, and tropical African patients. In Viruses and Tumors in Africans, edited by Williams AO, O'Connor GT, DeThe G, Johnson CA. p 749. New York, Oxford University Press, 1984
- 43. Fenoglio CM, Galloway DA, Crum CP: Herpes simplex virus and cervical neoplasia. In Progress in Surgical Pathology, edited by Fenoglio
- CM, Wolff M, p 45. New York, Masson, 1981 44. Biscegie AM, Rustgi VK, Hoofnagle JH, Dusheiko GM, Lotze MT: Hepatocellular carcinoma. Ann Intern Med 108:390, 1988
- 45. Beasley RP: Hepatitis B virus. Cancer 61:1942, 1987
- 46. Tiollais P, Pourcel C, Dejean A: The hepatitis B virus. Nature 317:489, 1985
- 47. Dunsford HA, Sell S, Chisari FV: Hepatocarcinogenesis due to chronic liver cell injury in hepatitis B virus transgenic mice. Cancer Res 50:3400, 1990
- 48. zur Hausen H: Papillomaviruses as carcinoma viruses. In Advances in Viral Oncology, edited by Klein G, Vol 8, p 1. New York, Raven Press, 1989
- 49. Friedell GH, Hertig AT, Younge PA: Carcinoma in Situ of the Uterine Cervix. Springfield, IL., CC Thomas, 1960
- 50. Clarke EA, Morgan RW, Newman AM: Smoking as a risk factor in cancer of the cervix:

- additional evidence from a case-control study. Am J Epidemiol 115:59, 1982
- 51. Thorley-Lawson DA: Immunological responses to Epstein-Barr virus infection and the pathogenesis of EBV-induced diseases.
- Biochim Biophys Acta 948:263, 1988 52. Klein G, Klein E: Conditioned tumorigenicity of activated oncogenes. Cancer Res 46:3211, 1986
- Yukawa K, Kikutani H, Inomoto T, Uehira M, Bin SH, Akagi K, Yamamura KI, Kishimoto T: Strain dependency of B- and T-lymphoma development in immunoglobulin heavy chain enhancer (Eμ)-myc transgenic mice. J Exp Med 170:711, 1989
- 54. Knutson JC, Sugden B: Immortalization of lymphocytes by Epstein-Barr virus: what does the virus contribute to the cell? In Advances in Viral Oncology, edited by Klein G, Vol 8, p 151. New York, Raven Press, 1989
- 55. Kripke ML, Borsos T: Immune surveillance revisited. JNCI 52:1393, 1974
- 56. Elliott BE, Carlow DA, Rodricks AM, Wade A: Perspectives on the role of MHC antigens in normal and malignant cell development. Adv Cancer Res 53:181, 1989
- 57. Schwartz RW: Another look at immunologic surveillance. N Engl J Med 293:181, 1975
- Baldwin RW: Immunological aspects of chemical carcinogenesis. Cancer Res 33:1, 1973
- 59. Purtilo DT: Defective immune surveillance in viral oncogenesis. Lab Invest 51:373, 1984
- 60. Purtilo DT, Linder J: Oncological consequences of impaired immune surveillance against ubiquitous viruses. J Clin Immunol 3:197, 1983
- 61. Ensoli B, Barillari G, Salahuddin SZ, Galo RC, Wong-Staal F: Tat protein of HIV-1 stimulates growth of cells derived from Kaposi's sarcoma lesions of AIDS patients. Nature 345:84, 1990
- 62. Gopas J. Rager-Zisman B. Bar-Eli M. Hämerling GJ, Segal S: The relationship between MHC antigen expression and metastasis. Adv Cancer Res 53:89, 1989
- 63. Mirvish SS: The etiology of gastric cancer: intragastric nitrosamide formation and other theories. JNCI 71:631, 1983
- Riddell RH, Goldman H, Ransohoff DF, Appelman HD, Fenoglio CM, Haggitt RC, Ahren C, Correa P, Hamilton SR, Morson BC, Sommers SC, Jardley JH: Dysplasia in inflammatory bowel disease: standardized classification with provisional clinical applications. Hum Pathol 14:931, 1983
- Dooley CP, Cohen H, Fitzgibbons PL, Bauer M, Appleman MD, Perez-Perez GI, Blaser MJ: Prevalence of Helicobacter pylori infection and histologic gastritis in asymptomatic persons. N Engl J Med 321:1562, 1989
- Lipkin M: Biomarkers of increased susceptibility to gastrointestinal cancer: new application to studies of cancer prevention in human subjects. Cancer Res 48:235, 1988
- 67. Reshef R, Rozen P, Fireman Z, Fine N, Barzilai M, Shasha SM, Shkolkik T: Effect of a

- calcium-enriched diet on the colonic epithelial hyperproliferation induced by N-methyl-N' nitro-N-nitrosoguanidine in rats on a low calcium and fat diet. Cancer Res 50:1764, 1990
- 68. Kato I, Kato K, Akai S, Tominaga S: A casecontrol study of gallstones: a major risk factor for biliary tract cancer. Jpn J Cancer Res 81:578, 1990
- 69. Connor DH: Tropical phagedenic ulcer. In The Skin, International Academy of Pathology Monograph 10, p 448. Baltimore, Williams & Wilkins, 1971
- 70. Potet F, Duchatelle V: Barrett's oesophagus. Curr Top Pathol 81:43, 1990
- 71. Price CHG: Primary bone-forming tumors and their relationship to skeletal growth. J Bone Joint Surg [Br] 40:574, 1958
- 72. Spjut HJ, Dorfman HD, Fechner RE, Ackerman LV: Tumors of bone and cartilage. In AFIP-Atlas of Tumor Pathology, p 174. Washington, DC, AFIP, 1971
- Committee on Biological Effects of Ionizing Radiations: Health Effects of Exposure to Low Levels of Ionizing Radiation. Washington. DC, National Academy Press, 1990
- 74. MacMahon HE, Murphy AS, Bates MI: Endothelial-cell sarcoma of liver following thorotrast injections. Am J Pathol 23:585, 1947
- 75. Hale KA, Ewing SL, Gosnell BA, Niewoehner DE: Lung disease in long-term cigarette smokers with and without chronic air-flow obstruction. Am Rev Respir Dis 130:716, 1984
- 76. Auerbach O, Garfinkel L: Histologic changes in the urinary bladder in relation to cigarette smoking and use of artificial sweeteners. Cancer 64:984, 1989
- 77. Johansson SL, Hirsch JM, Larsson P-A, Saidi J, Österdahl B-G: Snuff-induced carcinogenesis: effect of snuff in rats initiated with 4nitroquinoline N-oxide. Cancer Res 49:3063,
- 78. Tennant RW, Margolin BH, Shelby MD, Zeiger E, Haseman JK, Spalding J, Caspary W, Resnick M, Stasiewicz S, Anderson B, Minor R: Prediction of chemical carcinogenicity in rodents from in vitro genetic toxicity assays. Science 236:933, 1987
- Melnick RL, Boorman GA, Haseman JK, Montali RJ, Huff J: Urolithiasis and bladder carcinogenicity of melamine in rodents. Toxicol Appl Pharmacol 72:292, 1984
- 80. Heck HD'A, Tyl RW: The induction of bladder stones by terephthalic acid, dimethyl terephthalate, melamine (2,4,6-triamino-S-triazine), and its relevance to risk assessment. Regul Toxicol Pharmacol 5:294, 1985
- 81. Environmental Protection Agency. Melamine: toxic chemical release reporting: community right-to-know. In Federal Register, Vol 53, p 23128. Washington, DC, GPO, 1988 82. Ellwein LB, Cohen SM: The health risks of
- saccharin revisited. Crit Rev Toxicology 20:311, 1990
- 83. Mossman BT, Gee JBL: Asbestos-related diseases. N Engl J Med 320:1721, 1989

Cell Proliferation in Carcinogenesis

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Chemicals that induce cancer at high doses in animal bioassays often fail to fit the traditional characterization of genotoxins. Many of these nongenotoxic compounds (such as sodium saccharin) have in common the property that they increase cell proliferation in the target organ. A biologically based, computerized description of carcinogenesis was used to show that the increase in cell proliferation can account for the carcinogenicity of nongenotoxic compounds. The carcinogenic dose-response relationship for genotoxic chemicals (such as 2-acetylaminofluorene) was also due in part to increased cell proliferation. Mechanistic information is required for determination of the existence of a threshold for the proliferative (and carcinogenic) response of nongenotoxic chemicals and the estimation of risk for human exposure.

ERTAIN CHEMICALS HAVE LONG BEEN ASSOCIATED WITH cancer in humans, and animal models have been developed to study processes involved in the transition from a normal to a cancer cell (1). During the past two decades, emphasis has been shifting from the use of animal models primarily for the study of carcinogenic mechanisms to the use of animals to assay for carcinogenic potential of chemicals (2). Research has been directed more at quantitatively estimating the risk to humans. Traditionally, risk assessments have entailed the use of various mathematical and statistical formulations to extrapolate from results of high-dose animal bioassays to estimates of risk at low doses (3). However, high-dose tumor response data are inadequate for this purpose, as is most evident when efforts are made to predict a threshold below which there is no effect. These limitations indicate the need to base risk assessments on knowledge of the biology of tumor formation.

We have developed a model of carcinogenesis, based on biological data and principles, that we originally used as an analytical tool to interpret results of experiments with the bladder carcinogen N-[4-(5-nitro-2-furyl)-2-thiazolyl]formamide (FANFT) in rats (4). We demonstrated quantitatively that the tumorigenic effects of FANFT administration result from its dose-dependent genotoxic and proliferative effects, and that the proliferative effects operated only at the highest doses employed (4, 5).

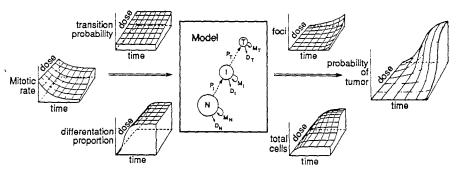
The model can be viewed as an assembly of dynamic relationships between variables that contribute to tumor production (Fig. 1), and incorporates several biological suppositions. A fundamental assumption is that cells exist within one of three states, normal, initiated (intermediate), or transformed, and that transitions between states occur or are irreversibly fixed only in replicating cells. These transitions are assumed to take place in a stochastic fashion and represent genetic changes introduced during cell replication, possibly with the involvement of oncogenes or tumor suppressor genes (6). Transformed cells are those that are malignant, not cells in benign lesions. In the absence of a genotoxic exposure, the probability of a transition occurring is small but not zero (thus accounting for spontaneous tumors). The likelihood of producing a cancerous cell is increased if either the probability of a genetic transition or the rate of cell replication is increased.

Another model that also incorporates the effect of cell proliferation and was validated using human epidemiology data lends further support for a two-event hypothesis for carcinogenesis (7). Although based on similar biological parameters, our model uses a different mathematical construct. To represent the biological dynamics within the target organ, we resorted to a recursive simulation. Beginning with its early development period, the status of the cell population in the target organ was computed in simulated time using the probabilities for each possible event (mitosis, genetic transition, or death) facing each cell within each of a series of specific time intervals. Calculations for each subsequent time interval incorporate the results of the preceding interval. The probabilities of mitosis or death are estimated by observation of cell proliferation and cell number at various times, and the probabilities of genetic transition were inferred by a comparison of model outcomes with

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Fig. 1. A mathematical model of carcinogenesis that entails two irreversible transitions, from normal (N), to initiated (I), to transformed (T) cell populations. Population mitotic rates, M_N , M_1 , and M_T , respectively, and cellular differentiation (and death) rates D_N , D_1 , and D_T are primary model inputs. The interaction of these rates determines the size of cell populations. Initiation and transformation transitions occur randomly during cell replication, represented by the probabilities p_1 and p_T . Model inputs are dependent on dose and animal age. Model outputs that can be validated with experimental data include target organ size (total number of cells), number of initiated cell foci (hyperplastic foci in the liver), and the proba-



bility of a visible tumor. The model is implemented computationally using stochastic simulation.

the observed time course of tumor development at the particular dose being simulated. Although this simulation approach precludes the possibility of directly estimating genetic transition probabilities and other experimentally unobservable model parameters using statistical inference, it does not risk the mathematical oversimplification required for the derivation of a computationally tractable expression that would relate tumor incidence to cellular proliferation and genetic transition variables. The quest for closed-form expressions is problematical because of the multiplicity of cellular states and the time- and dose-varying nature of the numerous cell behavior variables.

To illustrate the critical role of cell proliferation in carcinogenesis, we discuss here two prototypical compounds: a genotoxic carcinogen, 2-acetylaminofluorene (2-AAF), and a nongenotoxic agent, sodium saccharin.

2-Acetylaminofluorene (2-AAF)

To determine the tumorigenicity of 2-AAF at low doses, more than 24,000 female BALB/c mice were fed different doses (30 to 150 ppm) of 2-AAF for different periods of time (9 to 33 months) and killed at various intervals between 9 and 33 months of study (8). This "megamouse" experiment was designed to detect a 1% increase in the prevalence of tumors (thus is referred to as the ED₀₁ study) in two target organs, liver and urinary bladder. Rather than demonstrating how to extrapolate to low doses, this study raised additional questions (8-10). The dose-response curve for the liver was nearly linear down to the lowest amount administered, 30 ppm. In contrast, the dose-response curve for the bladder was nonlinear. At doses below 60 ppm, there was no detectable increase in bladder tumor prevalence compared to controls, whereas prevalence increased sharply at doses above 60 ppm. Examination of tumor response as a function of time complicated the issue further (9).

Initially, investigators postulated that the differences in doseresponse curves between liver and bladder could be explained by differences in 2-AAF toxicokinetics, and that binding of 2-AAF to DNA would not occur in the bladder below some threshold, whereas in liver even the lowest doses would have an effect. However, the administration of 2-AAF to BALB/c mice at similar and lower doses (5 to 150 ppm) produces a linear dose-response relationship for DNA adduct formation in both the liver and bladder (11).

The Armitage-Doll multi-stage model was also applied to explain the differences in 2-AAF response between liver and bladder tissues, leading to the postulation of a one-hit carcinogenic phenomenon for the liver and a three-hit process for the bladder (11). By accounting for the proliferative effects of 2-AAF in addition to its effects on

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DNA, which the Armitage-Doll model is unable to do, we are able to explain both dose-response curves using a two-event model of carcinogenesis (10).

Liver response to 2-AAF. In normal hepatocytes, 2-AAF is metabolized to its active, N-sulfated metabolite, which forms DNA adducts (11–13). This is reflected in our model by raising the probability of the first genetic event (p_I) above background. In contrast, cells in hyperplastic foci do not metabolize 2-AAF as readily, and considerably fewer DNA adducts are formed (12). Apparently, 2-AAF has a negligible effect on the probability of the second genetic event (p_T). At doses utilized in the ED₀₁ study, enlargement of the liver is not observed (8), providing evidence of no increased hepatocyte proliferation. Thus, the only apparent impact of 2-AAF on the liver was an increase in p_I over background levels; p_T and hepatocyte mitotic rates remained at background levels and were not affected by 2-AAF administration.

Mitotic rates in the normal adult liver are relatively low (labeling index $\leq 0.1\%$). During the high proliferative phase of organ development, occasional cells are likely to become initiated, even with a low, background value for p₁. The remainder of the animal's life can then provide sufficient opportunity for at least one of these initiated cells to progress to a transformed cell, and then proliferate to a tumor of detectable size. In the ED₀₁ study, spontaneous liver neoplasms were observed in 2.3% (n=383) of control mice sacrificed at 24 months and 34.8% (n=23) of mice sacrificed at 33 months (8), illustrating the influence of elapsed time on tumor development.

With a potent genotoxic compound such as 2-AAF, the relatively small number of cells initiated spontaneously during organ development is insignificant compared to the number initiated by reaction with 2-AAF metabolites (because of the increased p_1). The large number of initiated cells after exposure to 2-AAF, in combination with subsequent proliferation and transformation at background rates, results in an increased prevalence of liver tumors, particularly as the animal ages beyond 2 years (Fig. 2). At doses higher than those used in the ED01 study, 2-AAF also increases compensatory proliferation of surviving hepatocytes and sharply increases tumor prevalence as early as 6 months (13).

Bladder response to 2-AAF. Metabolism of 2-AAF in the liver also involves production of the N-glucuronide, which accumulates in the urine and is hydrolyzed to an electrophile that can react with both normal and initiated urothelial cells (11, 14). Thus, 2-AAF affects both p_I and p_T in the bladder. The relationship between 2-AAF dose and DNA adduct formation is apparently linear within the 5 to 150 ppm range (11). In contrast to the situation in liver, 2-AAF induces urothelial hyperplasia at doses \geq 60 ppm (Fig. 3) (8). Modeling the interaction of these responses to 2-AAF effectively duplicates the in vivo results (8, 10) (Fig. 2). Below 60 ppm, the apparent lack of increase in tumor prevalence reflects the minimum experimental

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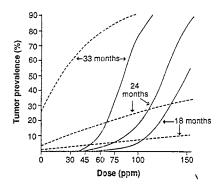


Fig. 2. Model results for effects of duration of exposure (18, 24, or 33 months) and 2-AAF dose on liver tumor (----) and bladder tumor (---) prevalence in mice. These analytical results have been demonstrated as being consistent with actual data from the ED₀₁ study (8, 10).

Fig. 3. Effect of normal growth, duration of exposure, and 2-AAF dose on total number of liver hepatocytes (----) and bladder urothelial cells (—) in mice. The increase in number of hepatocytes parallels the normal growth of the liver (10).



The increase in bladder cell number caused by 2-AAF is quantified from histopathology information from the ED₀₁ study (8, 10). 2-AAF administration began at approximately 1 month of age.

detection limit (1%) rather than the absence of tumors. At the higher doses, increased cell proliferation has an impact, and an increase in tumor formation occurs. From our modeling analyses of hypothetical situations, we calculated that if 2-AAF influenced only p₁ and p_T in the bladder, tumor prevalence at 24 months would be 4% at a dose of 150 ppm, whereas, if only cell proliferative effects were present, the corresponding tumor prevalence would be 6%. The prevalence with both operating simultaneously is 88%, suggesting a synergistic effect between genotoxicity and proliferation.

Sodium Saccharin

Dietary administration of high doses of sodium saccharin (NaS) to rats over two generations results in a significant increase in the frequency of bladder cancer, particularly in males (15, 16). In these two-generation studies, NaS feeding begins in the dam, is continued through gestation and lactation periods, then through the lifetime of the offspring. Subsequent experiments have shown that NaS administration beginning at birth results in essentially the same tumor prevalence as with NaS administration from conception (16), but NaS administration started after weaning usually produces an insignificant response (15, 16). However, if the post-weaning rat is first treated with a short regimen of a bladder carcinogen, such as FANFT, N-butyl-N-(4-hydroxybutyl)nitrosamine (BBN), or N-methyl-N-nitrosourea (MNU), followed by NaS, tumors result (5, 17).

Unlike 2-AAF, saccharin is nucleophilic, is not metabolized to a reactive electrophilic, does not react with DNA, and is not mutagenic in most short-term assays (17). However when NaS is administered to the rat at high dietary doses, proliferation in the urothelium increases, resulting in mild focal hyperplasia (17).

Role of cell proliferation. Modeling analyses demonstrate that NaS-induced cell proliferation is sufficient to account for the increase in bladder tumor prevalence after exposure to NaS (18). In the FANFT-NaS experiments, tumors are produced by the stimulating effect of NaS on the dynamics of a pool of FANFT-initiated cells. Because a nonzero probability of spontaneous genetic transforma-

tion (p_T) is associated with each mitosis of an initiated cell, an increase in the mitotic rate after exposure to NaS increases the number of opportunities for transformation.

In studies where NaS administration is not preceded by initiation with a genotoxic compound, it is possible to produce an increased number of initiated cells strictly by the increase in proliferation that occurs when NaS administration is begun early in the developmental period. Because the bladder already has a maximally proliferating epithelium during gestation (labeling index approximately 10%), NaS administration during the in utero period does not further increase the proliferation rate (17). However, during the 3 weeks after birth, the labeling index normally declines to <0.1%. Although relatively brief, this 3-week period is of disproportionate biological importance because approximately one-third of the total number of cell divisions in a rat's 2-year life-span occur during this period (18). A significant increase in cell proliferation rates during the 3 weeks after birth, coupled with the background probability of spontaneous genomic errors, can substantially increase the number of initiated cells. In assessing the carcinogenicity of nongenotoxic chemicals such as NaS, it is critical to consider the increased number of initiated cells generated during fetal and neonatal development and the resulting increase in tumor prevalence to experimentally detectable levels (17).

An increase in the number of initiated cells caused only by excess proliferation has also been demonstrated in male rat bladders after weaning. The epithelium was ulcerated by freezing, and the resultant burst of mitotic activity was comparable to that seen during fetal development (19). Within 3 to 4 weeks the epithelium healed and returned to mitotic quiescence and normal morphology. Nevertheless, if high doses of NaS are subsequently administered, bladder tumors result. In terms of our model, a sufficient number of initiated cells are generated spontaneously during the regenerative hyperplasia such that the increased and sustained proliferative activity induced by NaS generates tumors (18, 19).

Proliferative mechanism and threshold. Utilizing traditional risk assessment methods, the results described above in male rats with extremely high doses of NaS can be extrapolated to arrive at an approximate calculated risk for humans exposed to low doses of NaS (20). However, there is clearly a need to understand the underlying mechanisms of carcinogenesis by nongenotoxic compounds before any rational estimate of human risk can be made. The complexity of the task in risk assessment is indicated by the finding that female rats are much less susceptible to bladder tumorigenesis in response to NaS than males, and mice, hamsters, and monkeys are resistant even at high doses (15, 17).

The different salt forms of saccharin produce markedly different urothelial proliferative responses (21). Potassium saccharin somewhat increases urothelial proliferation relative to controls, but less than does NaS. Urothelial proliferation after treatment with calcium saccharin and acid saccharin is statistically indistinguishable from controls; thus it might be assumed that neither calcium saccharin nor acid saccharin would be carcinogenic in the rat model. Absorption and urinary excretion of the saccharin anion is similar regardless of which form of saccharin is administered, but the physiological changes in the urine associated with the high loads of the different salts produce marked differences in urinary pH, ion concentrations, volume, and osmolality. The changes in pH and salt concentrations do not alter the ionic structure of saccharin, and there is no evidence that saccharin interacts directly with a urothelial cell receptor (17). A similar increased proliferative and tumorigenic activity in the male rat urothelium following chemical initiation is seen with high dose of several other sodium salts of weak to moderate organic acids, many of which are naturally occurring and essential for the wellbeing of living organisms, including vitamin C, glutamate, and

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bicarbonate (5, 17). No tumorigenicity is observed when the acid form of these chemicals was tested (5, 17).

We have recently observed that, in addition to the normally present MgNH'₄PO₄ crystals, many crystals in the urine of rats fed high doses of NaS contain silicate, and a large amount of a flocculent precipitate that contains silicate is also present (22). The silicate crystals and precipitate appear to act as microabrasives or cytotoxic material for urothelial cells, resulting in focal necrosis and consequent regenerative hyperplasia. Silicate precipitate and crystals require protein for their formation (23). Saccharin binds to urinary protein, particularly α_{2u} -globulin (24), thus enhancing the precipitation and crystallization that only occasionally occurs in control male rats (25). Urinary acidification inhibits silicate precipitation and inhibits the proliferative effects of NaS. High levels of urinary sodium and protein enhance silicate precipitation (23). The principal factor that appears to predispose the male rat to silicate crystal formation following NaS feeding is the presence of large quantities of normally occurring urinary protein, especially the protein specific to the male rat, α_{2u} -globulin (24). The female rat has much less urinary protein that the male and is less responsive to the proliferative and tumorigenic effects of NaS on the urothelium. The mouse, a species that is not responsive to saccharin even at NaS levels of 7.5% of the diet (at least three times the apparent threshold level in male rats), has low levels of urinary protein and did not form silicate crystals when fed NaS (25).

The multiple physical-chemical parameters in the male rat suggest that a fairly high threshold exists for NaS dose in producing silicate crystals. It is extremely unlikely that the silicate precipitates and crystals would form in humans under normal conditions of NaS ingestion, since human urine has very little protein and has less sodium than rat urine. This is consistent with the general lack of an association in humans between NaS ingestion and bladder cancer or hyperplasia (20, 26, 27).

Classification of Chemicals for Human Risk Assessment

The current practice is to classify chemicals as initiators, promoters, complete carcinogens, or progressing agents. In light of the demonstrated ability of compounds to increase the risk of cancer by either directly altering DNA, increasing cell proliferation, or both, distinctions blur and traditional terminology is inadequate. We feel it is useful to classify chemical carcinogens into those that interact with DNA (genotoxic) and those that do not (nongenotoxic) (Fig. 4) (28). Many of the latter chemicals act by increasing cell proliferation, either by direct mitogenesis of the target cell population or by cytotoxicity and consequent regenerative proliferation. Genotoxic chemicals (2-AAF and numerous others, such as diethylnitrosamine, dimethylnitrosamine, and FANFT) usually do not exhibit a threshold for the interaction with DNA, and, at higher doses, may cause cell death resulting in cell proliferation (5, 29). This dual effect of genotoxic chemicals frequently leads to a dose-response curve similar to that of 2-AAF in the bladder described above. A modest rate of increase in tumor prevalence at low doses is due only to a genotoxic effect, and a much greater rate of increase at higher doses is due to the synergistic influence of increased cell proliferation. The actual dose- and time-response for a chemical is dependent on whether the compound has a genotoxic effect, a proliferative effect, or both, and whether it affects normal or initiated cells, or both.

The nongenotoxic chemicals can be further categorized by their mechanisms of action, if known. For example, phorbol esters, dioxin, and hormones each interact with a cellular receptor (30), whereas NaS (17), antioxidants (31), thin films, hepatotoxins, and

nephrotoxins (28) act through a non-receptor mechanism. Cytotoxicity, direct mitogenesis, or both can also occur with chemicals acting through cell receptors (such as the phorbol esters) (28, 30). Compounds acting through specific receptors tend to be active at low doses, and it is unclear whither a no-effect threshold could be ascertained for these compounds. Similarly, chemicals that are directly mitogenic to target cells may or may not have a threshold. In contrast, most, if not all, compounds that act solely through a cytotoxic mechanism would be expected to have a no-effect threshold above which cytotoxicity becomes apparent. Below the threshold, cytotoxicity and increased cell proliferation would not occur, and there would be no increased risk of tumors. Interpretation of long-term bioassays for nongenotoxic chemicals must take into account aspects of nonreceptor mechanisms.

Examples of a dose-response threshold occur with uracil and melamine (32). If sufficiently high doses of either of these nongenotoxic chemicals are fed to rats or mice, urinary calculi, urothelial proliferation, and tumors occur. If the dose is below the minimum at which calculi occur, there is no increased cell proliferation or tumor formation.

Cell Proliferation as a Predictor of Carcinogenesis

Despite the importance of cell proliferation in carcinogenesis, short-term assays of increased cell proliferation in response to nongenotoxic chemicals are likely to prove as inadequate as short-term genotoxicity assays for predicting carcinogenicity. Some chemicals induce only a temporary or mild increase in proliferation that may not be adequate to produce a detectable increase in tumor prevalence within the lifetime of the experimental animal. Also, increased proliferation must occur in cells susceptible to cancer development, rather than in nonsusceptible cells, such as terminally differentiated cells, that may also be present in the target organ. For example, turpentine can cause proliferation of the skin, but is a very weak skin tumor promoter (33). Turpentine primarily increases proliferation of the keratinocytes rather than the dark basal cells that are the apparent precursors of skin tumors.

Confusion can also arise with chemicals such as cyclophosphamide (34). Although it is extremely cytotoxic to the bladder epithelium, leading to a marked regenerative hyperplasia, it is also

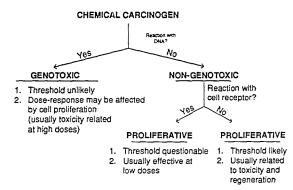


Fig. 4. Proposed classification scheme for carcinogens. The effect of genotoxic chemicals can be accentuated if cell proliferative effects are also present. Nongenotoxic chemicals act by increasing cell proliferation directly or indirectly, either through interaction with a specific cell receptor or nonspecifically by (i) a direct mitogenic stimulus; (ii) causing toxicity with consequent regeneration; or (iii) interrupting physiological process. Examples of the latter mechanism include TSH stimulation of thyroid cell proliferation after toxic damage to the thyroid, and viral stimulation of proliferation after immunosuppression.

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cytotoxic to any bladder tumor cells that might form. If cyclophosphamide is administered at doses high enough to be genotoxic but below those that are cytotoxic, the prevalence of bladder tumors is increased in animals and humans. At higher cytotoxic doses, regenerative hyperplasia occurs but no tumors are produced.

There are numerous indications in humans that prolonged, increased cell proliferation is necessary for the development of tumors, particularly for hormonally related tumors such as estrogenrelated endometrial carcinomas (35). It appears that most virally related human tumors are also a result of sustained increased proliferation. For example, Epstein-Barr virus (EBV) stimulates B lymphocyte proliferation. When a patient is immunosuppressed, whether due to heredity, immunosuppressive drugs associated with transplantation, or AIDS, the B-cell proliferation cannot be controlled, and there is an appreciable increase in the risk of B-cell lymphomas (36). Hepatitis B virus (HBV) can produce chronic hepatitis and cirrhosis, characterized by persistent necrosis and regenerative hyperplasia, and is also associated with an increased incidence of hepatoma (37).

It would appear that increased cell proliferation also contributes to the development of tumors secondary to various chemical exposures in humans. For example, cigarette smoking is known to cause bladder cancer in humans, perhaps due to a hyperplastic effect on the urothelium of many cigarette smokers, in addition to the probable genotoxic damage that occurs (27).

As the mechanisms of carcinogenesis become more thoroughly understood, a more rational approach can be taken for extrapolation from high dose experimental data in animals to low dose natural exposure and assessment of the risk faced by human populations exposed to chemical agents. The effects of toxicity and consequent cell proliferation are particularly critical for nongenotoxic agents, because a threshold effect is likely.

REFERENCES AND NOTES

- 1. E. C. Miller and J. A. Miller, Cancer 47, 2327 (1981).
- 2. L. S. Gold et al., Environ. Health Perspec. 58, 9 (1984); L. S. Gold et al., ibid. 67, 161 (1986); L. S. Gold et al., ibid. 74, 237 (1987); L. S. Gold et al., ibid. 84, 215
- J. Van Ryzin, Biometrics (Suppl.) 38, 130 (1982).
- R. E. Greenfield, L. B. Ellwein, S. M. Cohen, Carcinogenesis 5, 437 (1984); L. B. Ellwein and S. M. Cohen, in Biologically-Based Methods for Cancer Risk Assessment, C. Travis, Ed. (Plenura, New York, 1989), pp. 181–192.

 5. S. M. Cohen and L. B Ellwein, Toxicol. Lett. 43, 151 (1988).

 6. R. A. Weinberg, Camer Res. 49, 3713 (1989).

- A. G. Knudson, Proc. Natl. Acad. Sci. U.S.A. 68, 820 (1971); S. H. Moolgavkar and D. J. Venzon, Math. Biosci. 47, 55 (1979); S. H. Moolgavkar and A. G. Knudson, Jr., J. Natl. Cancer Inst. 66, 1037 (1981).

- 8. J. A Staffa and M. A. Mehlman, J. Environ. Path. Toxicol. 3, 1 (1980).
- F. W. Carlborg, Food Cosmet. Toxicol. 19, 367 (1981); Society of Toxicology, Fundam. Appl. Toxicol. 3, 26 (1983); D. H. Hughes et al., ibid., p. 129; P. Shubik, ibid., p. 137; D. Krewski et al., ibid., p. 140; L. N. Park and R. D. Snee, ibid., p. 320; K. G. Brown and D. G. Hoel, ibid., p. 458; ibid., p. 470; R. L. Kodell et al., ibid., p. 9a; R. D. Bruce et al., ibid., p. 9a.
- S. M. Cohen and L. B. Ellwein, Toxicol. Appl. Pharm. 104, 79 (1990).
 F. A. Beland, N. F. Fullerton, T. Kinouchi, M. C. Poirier, IARC (Int. Agency Res. Cancer) Sci. Publ. No. 89 (1988), p. 175.
- E. Farber, S. Parker, M. Gruenstein, Canter Res. 36, 3878 (1976); R. C. Gupta, K. Earley, F. F. Becker, ibid. 48, 5270 (1988); C. C. Lai, J. A. Miller, E. C. Miller, A. Liem, Carcinogenesis 6, 1037 (1985).
- 13. N. A. Littlefield, C. Cipiano, Jr., A. K. Davis, K. Medlock, J. Toxicol. Env. Health 1, 25 (1975).
- 14. F. F. Kadlubar, J. A. Miller, E. C. Miller, Cancer Res. 37, 805 (1977)
- D. L. Arnold et al., Toxicol. Appl. Pharmacol. 52, 113 (1980); IARC (Int. Agency Res. Cancer) Monogr. Eval. Carcinog. Risk Chem. Hum. 22, 111 (1980).
 G. P. Schoenig et al., Food Chem. Toxicol. 23, 475 (1985).
 L. B. Ellwein and S. M. Cohen, Crit. Rev. Toxicol. 20, 311 (1990).
 _____, Risk Analysis 8, 215 (1988).
 G. Murasaki and S. M. Cohen, Cancer Res. 43, 182 (1983); R. Hasegawa, R. E.

- Greenfeld, G. Murasaki, T. Suzuki, S. M. Cohen, ibid. 45, 1469 (1985).
 B. K. Armstrong, IARC (Int. Agency Res. Canter) Sci. Publ. No. 65 (1985), p. 129;
 D. Krewski, ibid., p. 145; R. W. Morgan and O. Wong, Food Chem. Toxicol. 23, 529 (1985); F. W. Carlborg, ibid., p. 499.
 R. Hasegawa and S. M. Cohen, Canter Lett. 30, 261 (1986).
- 22. S. M. Cohen, M. Cano, E. M. Garland, R. A. Earl, Proc. Am. Assoc. Cancer Res. 30, 204 (1989).
- C. B. Bailey, Can. J. Biochem. 50, 305 (1972); C. J. Schreier and R. J. Emerick, J. Nutr. 116, 823 (1986); R. J. Emerick, Nutr. Rep. Int. 34, 907 (1986); J. Nutr. 117, 1924 (1987).
- J. A. Swenberg, B. Short, B. Borghoff, J. Strasser, M. Charbonneau, Toxitol. Appl. Pharm. 97, 35 (1989).
- 25. S. M. Cohen et al., unpublished observations.
- 26. R. N. Hoover and P. H. Strasser, Lancet i, 837 (1980).
- 27. O. Auerbach and L. Garfinkel, Cancer 64, 983 (1989).
- 28. B. E. Butterworth and T. J. Slaga, "Nongenotoxic Mechanisms in Carcinogenesis,"
- Banbury Report No. 25 (1987).
 29. R. Peto, R. Gray, P. Benton, P. Grasso, IARC (Int. Agency Res. Cancer) Sci. Publ.
- No. 57 (1985), p. 627.
 A. Poland and E. Glover, Mol. Pharmacol. 17, 86 (1980); V. Solanki and T. J. Slaga, in Mechanisms of Tumor Promotion, T. J. Slaga, Ed. (CRC Press, Boca Raton, FL, 1984), vol. 2, p. 97; A. L. Brooks, S. W. Jordan, K. K. Bose, J. Smith. D. C. Allison, Cell Biol. Toxicol. 4, 31 (1988); R. N. Hill, Fundam. Appl. Toxicol. 12, 629
- N. Ito and M. Hirose, Adv. Cancer Res. 53, 247 (1989).
 J. W. Jull, Cancer Lett. 6, 21 (1979); T. Shirai, E. Ikawa, S. Fukushima, T. Masui, N. Ito, Cancer Res. 46, 2062 (1986); H. D'A. Heck and R. W. Tyl, Regulat. Toxicol. Pharmacol. 5, 294 (1985).
- R. K. Boutwell, Prog. Exp. Tumor Res. 4, 207 (1964).
 M. S. Soloway, Cancer 36, 333 (1975); L. A. Levine and J. P. Richie, J. Urol. 141, 1063 (1989)
- A. Paganini-Hill, R. K. Ross, B. E. Henderson, Br. J. Cancer 59, 445 (1989).
 D. T. Purtilo and T. Osato, AIDS Res. 2, 1 (1986).
- 37. R. P. Beasley, Cancer 61, 1942 (1988).
- 38. We thank the late R. Greenfield, our colleagues, and technologists for their contributions, and G. Philbrick for assistance with this manuscript. Supported by grants CA32513, CA28015, and CA36727 from the National Cancer Institute, by the Department of Health, State of Nebraska, and by the International Life Sciences Institute-Nutrition Foundation.

Applications of Expert Judgment

Moeller

THE ROLE OF EXPERT JUDGMENT IN RISK ANALYSIS

- 1. USE OF EXPERT JUDGMENT IN RISK ANALYSIS
 - a. There is no Question That Expert Judgment is Needed; The Only Question is Whether to Use It Explicitly
 - b. It Requires No More Use of "Art" Than Any Other Field
 - c. Expert Judgment May Not Provide the Solution; However, It Will Often Show You Where and How to Seek It
 - d. Properly Applied, Expert Judgment Can Assist In:

Identifying Decision Alternatives; Validating Analytical Models; Assessing Influencing Parameters

Note: False Assumptions Relative to A Parameter, Such as Its Degree of Independence, Can Significantly Affect The Final Results

- e. Expert Judgment Should Reflect Current Knowledge and Quantify Attendant Uncertainties; While the Additional Information Provided Will Help Reduce Ignorance, It Will Not Necessarily Reduce Uncertainty
- f. Although Expensive, Its Use "Up Front" Can be Very Cost-Effective in Terms of the Avoidance of Delays and Associated Costs at Later Stages

2. HOW MUCH DATA ARE SUFFICIENT

- a. Expert Judgment is not a Substitute for Data When It can be Readily Obtained
- b. Expert Judgment Should Follow Only After an Agreed Upon Level of Effort to Perform Additional Scientific Studies, and to Analyze and Evaluate the Resulting Data, Has Been Met

3. OBSERVATIONS ON THE USE OF EXPERT JUDGMENT

- a. It Is Well Established as a Tool in Risk Analysis
- b. Its Use is Mandatory Where Data are Inadequate; However, It Should Not Be Used as a Replacement for "Hard" Data
- c. Proper Application of Expert Judgment Requires Care, Planning, Documentation, and Resources. Protocols for Elicitation Should Be Systematic, Visible, and Easily Understood
- d. It Should Not Be Conducted as Simply a Poll of Experts; It Should Include Explicit Articulation of the Principles, Reasoning, and Data on Which the Judgments are Based
- e. Its Formal Solicitation Can and Should Clearly Explicate the Uncertainties for the Decisionmakers; At the Same Time, It Should be Recognized That Such Judgments Represent Only "Snapshots" in Time of Prevelant Opinion; They Are Not a Means for "Revealing" Truths
- f. The Methodology Used Can Significantly Influence the Result of the Process; Key Factors Include:

Identification and Selection of Issues;
Identification, Selection, and Use of Experts
and Solicitors;
The Biases of the Expert and Elicitors;

The Biases of the Expert and Elicitors; The Methods for Aggregating the Results

- g. An Important Issue is Estimating the Magnitude of the Uncertainty, Especially Where Data Are Limited
- h. In All Cases, the Selected Approach (or Conclusion)
 Should be Justified; The Most Conservative Approach
 Should Not Necessarily Be Chosen Simply Because the
 Data Are Inadequate

4. OBSERVATIONS FROM PAST USE OF EXPERT PANELS

- a. There Is Always a Lack of Sufficient Time for Adequate Iteration With the Experts on Their Results
- b. The Definition of Issues is Always Critical; This Involves a Balance Between the Freedom of the Expert and Overdefining and Overconstructing the Issues
- c. Anonymity Should be Avoided; Knowledge of the Sources of Specific Opinions Improves The Defensibility of the Results
- d. Each Expert Should be Encouraged to Analyze the Questions Indepth Prior to the Panel Being Convened
- e. A Full Range of Weighting Strategies Should be Evaluated in Aggregating the Results

5. QUESTIONS TO BE CONSIDERED IN THE USE OF EXPERT JUDGMENT

- a. How Should the Experts Be Identified and Selected?
- b. What Are The Preferred Methods for Using Formal Expert Judgment? How are the Mechanics of the Elicitations to be Carried Out?
- c. How Are the Pertinent Issues and Questions to be Selected?
- d. What Are The Pitfalls Associated With the Use of Expert Judgment? For Example, How Can Biases (Institutional and Motivational) Be Evaluated and Reduced?
- e. Is Dependency Among Experts (Mutual Influence) Desirable?
 If so, What Are the Appropriate Ways to Encourage It?
 If not, How Can It Be Minimized or Eliminated?
- f. Are There Appropriate Protocols for Weighting the Judgments of Experts and for Weighting Alternative Models and Their Results? If so, What Are the Criteria for Assigning Weighting Factors?
- g. How Should Judgments Be Aggregated? What Are The Criteria for Choosing an Aggregation Method?
- h. What is the Appropriate Level of Documentation for the Elicitation?
- i. What Steps Should be Taken to Control the Potential Influence of Normative Experts on the Outcome?

6. QUESTIONS ON ELICITATIONS FROM SINGLE EXPERTS

- a. Lack of Benefit of Interaction with Peers
- b. Assumptions Underlying Judgments May Not Be Articulated
- c. Expert May be More Subject to Motivational and Cognitive Biases
- d. Quantification of Uncertainty Will Generally be Less
- e. Results May be Less Defensible; A Single Expert (Versus a Panel) May Have Less Credibility With Outside Groups

7. SELECTION AND ORGANIZATION OF PANEL MEMBERS

a. They Can Be Selected on the Basis of:

Their Publications;
Their Relevant Experience;
Their Experimental Knowledge;
Their Degree of Cooperation; and
The Input From Outside Groups
(These Can Be Solicited by Mail
or Through an RFP)

b. Should They Be Organized Horizontally of Vertically?

Vertical Interaction is Helpful; Horizontal May Make Interfaces Difficult (They Must Interact to Exchange Information at Each "Nodal" Point)

8. TRAINING OF PANEL MEMBERS

- a. Is Required for Essentially All Panel Members
- b. Should Be Designed to Sensitize the Experts on How Their Information Will be Used and How It Could Be Abused
- c. Should Recognize That Motivational Biases (Hidden Agenda) Are Less Responsive Than Cognitive Biases

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- 9. PITFALLS AND ADVANTAGES OF THE PANEL APPROACH
 - a. Dominant Personalities May Heavily Influence the Results:

Avoid by Having Each Member Formally Document His/Her Opinion and Rationale;

Experts Can Also Be Required to Construct Probability Distributions for Their Positions

The Greatest Sources of Bias Are Unstated Assumptions

b. To Avoid Criticism, It is Often Necessary to Use "Experts" With Relatively Shallow-Knowledge of the Subject:

This May Require Training That Can Introduce Biases

c. To Overcome Biases, Panels Can be Made Up of Experts With Diverse Perspectives:

While This Can Remove Some of the Biases, It May "Fix" the Results

- 10. BENEFITS OF THE PANEL APPROACH
 - a. All Members Can Be Provided the Same Information
 - b. Approach or Thoughts of Each Will Be Transparent for Other Members to Review
 - c. Positions Will Change As a Result of New Information Provided and Group Dynamics

11.

STEPS IN THE PANEL PROCESS

- a. The Issues Must be Identified and Selected
- b. The Experts Must be Identified and Selected
- c. The Issues Must be Discussed and Refined
- d. The Experts Must be Trained for Elicitation
- e. The Information Must be Elicited
- f. The Results Must be Analyzed and Aggregated, and Disagreements Resolved
- h. The Results Must Be Documented and Communicated to the Needed Parties

12.

GUIDANCE FOR GOOD PANEL OPERATIONS

- a. Ambiguity Can Be Minimized by Making the Questions Specific
- b. If Final Conclusions Are to be Aggregated, They Must Be in the Same Format
- c. If an Expert Has Difficulty Quantifying an Answer,
 Decompose the Question for Which He/She Can Construct
 Answers

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13.

GUIDANCE ON PANEL METHODOLOGY

- a. The Methodology Must Allow Different Experts to Share Each Others' Information so that Each Expert Can Base His/Her Ultimate Judgment on a Common Set of Information
- b. The Methodology Must Provide for Significant Interactions Among the Experts, So That They Can Share Different Perspectives and Approaches
- c. The Methodology Must Allow The Experts to Define or Redefine the Questions Being Asked, So That They Can Answer the Questions in Their Terms
- d. The Methodology Must Lead to the Conduct of the Proceedings in a Manner so as to Motivate the Experts
- e. The Methodology Must Provide Structured Ways in Which "Biases" (Different Perspectives) Can Be Identified, Brought to the Surface, and Subjected to Scrutiny
- f. The Methodology Must Allow Sufficient Time so That the Experts Can Perform Their Own Research and Analysis; Usually This Calls for Two Iterations in the Elicitation
- g. The Methodology Must Recognize That the Questions Being Addressed Do Not Have One "Correct" Answer, or Even "One" Correct Approach
- h. The Methodology Must Provide Full Documentation of What Happened, What Factors Underlie the Judgments of Each Expert, and Why; This Means That Each Expert Must be Comfortable With the Way in Which His/Her Judgment is Documented

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14. AGGREGATION OF CONCLUSIONS OF INDIVIDUAL PANEL MEMBERS

- a. The Opinions of "Mainstream" Experts Can be Requested to Evaluate the Expertise of Individual Panel Members
- b. If a Rationale Exists to Reject the Opinion of One or More Panel Members, This Can Be Done; However, Any Quick Ploy to Remove Dissenting Opinion Must Be Avoided
- c. Oftentimes It is Important to Retain the Component Contributions of Individual Panel Members, Even if Only One Aggregated Result is Needed in the Particular Application
- d. Forced Consensus Compromises the Defensibility of the Results

15. DOCUMENTATION OF THE ELICITATION

- a. It Should Include Unambiguous Specification of the Events for Which Probabilities Were Assessed
- b. The Assessed Probabilities for Those Events Should be Clearly Expressed
- c. The Data, Reasoning, Models, and Calculations Used in the Assessments Should be Documented, As Well As How and Why They Were Used
- d. The Documentation Should Also Include a Rational Basis for Eliminating and/or Not Documenting Any Information That Was Considered to be "Obvious"

16.

CONCLUSIONS

- a. Expert Judgment is a Necessary Part of Risk Analysis
- b. Expert Judgment Must be Applied in Both an Explicit and Implicit Manner, With a Reasonable Division Between the Two
- c. The Final Product Should Include Detailed Information on the Principles, Rationale, and Data On Which the Conclusions are Based
- d. Where There are Major Weaknesses in the Experimental Data, the "Strengths" of Expert Judgment Can Be Extremely Helpful
- e. Explicit Expert Judgment is Primarily Designed to Aid in Decision Making; It is Not There Solely to Provide a "Warm Fuzzy Feeling"

17. OTHER CONCLUSIONS

- a. Where the Reasoning Process Can Be Understood (and Accepted by Other Reasonable People), A Decision Based on Expert Judgment Should Stand Up in the Courts
- b. Although the Process of Solicitation of the Experts is Important, the Legal System Will Be More Interested in the Facts and Rationale for the Decision
- c. The Primary Purpose of Expert Judgment is to Provide a Foundation on Which the Decisionmakers Can Act
- d. Expert Judgment is Always Subject to Change and Should be Interpreted Accordingly

Reference:

Bonano, E. J., Hora, S. C., Keeney, R. L., and von Winterfeldt, D., "Elicitation and Use of Expert Judgment in Performance Assessment for High-Level Radioactive Waste Repositories," Report NUREG/CR-5411, U.S. Nuclear Regulatory Commission, Washington, DC (May, 1990).

The Respiratory System as an Entry for Exposure

Valberg

The Respiratory Tract as a Route of Exposure

- I. Major surfaces of the body: skin, respiratory tract, gastrointestinal tract.
 - A. Histology and thickness of skin
 - B. Absorption of materials from the GI tract.
 - C. Basic anatomy and histology of the respiratory tract.
- II. Review of Particulate Deposition
 - A. Forces acting to deposit particles in the lungs:
 - 1. Inertia.
 - 2. Gravitation.
 - 3. Diffusion.
 - 4. Interception.
 - B. Factors determining the effectiveness of these forces:
 - 1. Aerosol characteristics.
 - 2. Parameters of respiration.
 - 3. Anatomy of the respiratory system.
 - C. Predicting deposition of particles in the lungs.
- III. Lung Clearance Mechanisms
 - A. Clearance from the ciliated regions of the lungs: mucus transport.
 - 1. Frequency and quality of the ciliary beat.
 - 2. Quantity and rheological properties of the mucus.
 - B. Clearance of particles from the non-ciliated regions of the lungs.
 - 1. Role of alveolar macrophages.
 - 2. Lymphatic drainage.
 - 3. Permanent stores.
 - C. Uptake and distribution of inhaled gases.
- IV. Fate of Toxic Materials that Enter the Body
 - A. The Circulation.
 - 1. Anatomy and physiology.
 - 2. Overall patterns.
 - B. Elimination: transfer of materials back to the outer environment.
 - 1. Via lungs.
 - 2. Via gut.
 - 3. Via kidney.
 - C. Metabolic changes and detoxification mechanisms.

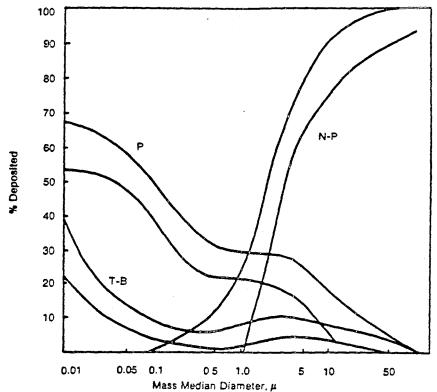
I. The Respiratory Tract

Human lung surfaces, because of their primary function of gas exchange, are brought into intimate contact with irritating gases and airborne particles. The mass of air we inhale each day far exceeds the mass of material entering into our GI tract. The same thinness and extensive area that qualify the air-blood barrier for the rapid exchange of oxygen and carbon dioxide reduce its effectiveness as a barrier to inhaled micro-organisms, allergens, carcinogens, toxic particles, and noxious gases. Inhalation of these agents can initiate or at least aggravate chronic obstructive lung disease. Particularly in the cases of cigarette smoking and occupational exposures, the health consequences of particle deposition and toxic gas uptake are increasingly being demonstrated. To assess adequately the risk of a particular exposure, an understanding of the factors involved in the deposition and clearance of inhaled substances is needed. Therefore, the mechanisms which are pertinent to particle deposition and clearance will be described, and the relationship of these respiratory defense mechanisms to the pathogenesis of lung disease will be presented.

II. Review of Deposition:

- A. Deposition is the process that determines what fraction of inspired particulates will be caught in the respiratory tract and thus fail to exit with the expired air. Several distinct processes following physical laws operate to move particles suspended in the inspired air toward the surface of the respiratory tract: inertial forces, sedimentation, Brownian diffusion, and interception. It is likely that all particles deposit upon touching a surface, and thus the site of initial deposition is the site of contact.
 - 1. Inertia refers to the tendency of moving particles to resist changes in direction and speed. Repeated branching in the airways cause sudden changes in the direction of air-flow; however, because of inertia, particles tend to continue in their original direction, crossing air-flow streamlines and eventually impacting on the airway walls.
 - 2. Gravity accelerates falling bodies downward, and terminal settling velocity is reached when viscous resistive forces are equal and opposite in direction to gravitational forces. Respirable particles reach this constant terminal or sedimentation velocity in less than 0.1 msec. Thus, particles are also removed as their terminal velocity causes them to strike the airway walls or alveolar surfaces.
 - 3. Aerosol particles also undergo Brownian diffusion, a random motion caused by collisions of gas molecules with particles suspended in the air; this motion also causes the particles to cross streamlines and reach lung surfaces where they will deposit.
- B. The effectiveness of these deposition mechanisms depends on: (1) the size distribution of aero-dynamic diameters of the particles, (2) the pattern of breathing, and (3) the anatomy of the respiratory tract. These factors will determine not only the fraction of the inhaled particles that are deposited but also the site of deposition.
 - 1. The effective aerodynamic diameters of particles determine the magnitude of forces acting on them. For example, while inertial and gravitational effects increase with increasing particle size, diffusion produces larger displacements as particle size decreases. Effective aerodynamic diameter is a function of particle size, shape, and density. In order to predict deposition patterns, it is essential to describe the distribution of aerodynamic diameters of particles in the aerosol. Two commonly-used parameters summarizing the size distribution are the mass median aerodynamic diameter (MMAD) and the geometric standard deviation (GSD).

- 2. Another factor modulating site and amount of deposition is breathing pattern. Minute volume defines the average flow velocity of the aerosol-containing air in the lung and the total number of particulates to which the lung will be exposed. Increasing the velocity of gas flow enhances deposition by inertial impaction. Respiratory frequency will affect the residence time of aerosols in the lungs and hence the probability of deposition by gravitational and diffusional forces. Changing lung volume will alter the dimensions of the airways and parenchyma.
- 3. The anatomy of the respiratory tract is important since it is necessary to know the diameters of the airways, the frequency and angles of branching, and the average distances to alveolar walls. For a given inspiratory or expiratory flow rate, airway anatomy determines local linear velocity of the air stream and the character of the flow. A significant change in the effective anatomy of the respiratory tract occurs when there is a switch between nose and mouth breathing. In addition to warming and humidifying the air, the nose prevents penetration of large particles and highly soluble gases to the remainder of the respiratory system. The narrow cross section of the airway here results in high linear velocities. The sharp bends in direction of airflow and the nasal hairs both promote impaction of aerosols. Particle deposition exhibits variability due to inter- and intra-species differences in lung morphometry; even within the same individual, the dimensions of the respiratory tract vary with changing lung volume, with aging, and with pathological processes.
- C. The ICRP lung model (See reference 5) provides some predictions for the percentage deposition of particles for an adult human breathing a 1,450 ml tidal volume, 15 times a minute. Deposition in the nasopharynx ranges from 50.2% of the inspired particles with 2.0 μm MMAD to 95.6% of 20 μm particles. Deposition in the tracheobronchial compartment decreases from 3.6 to 1.0% as the MMAD increases from 2.0 μm to 20 μm and finally, deposition in the pulmonary compartment decreases from 21 to 2.6% as MMAD increases from 2.0 μm to 20.0 μm. The predictions of the ICRP lung model are summarized in the graph below:



-Aerosol deposition in respiratory tract. Tidal volume is 1,450 ml; frequency, 15 breaths per minute. Variability introduced by change of sigma, geometric standard deviation, from 1.2 to 4.5. Particle size equals diameter of mass median size. (Adapted from Task Group on Lung Dynamics')

III. Lung Clearance Mechanisms:

Clearance refers to the dynamic processes that physically expel particulates from the respiratory tract; it is the output of particulates previously deposited. Highly soluble particles dissolve rapidly and are absorbed into the blood from the respiratory tract. Their metabolism and excretion resemble that of an intravenously injected dose of the same material.

A. Ciliated Regions

- 1. Less soluble particles that are deposited on the mucus blanket covering pulmonary airways are moved toward the pharynx by the cilia. Also present in this moving carpet of mucus are cells and particles which have been transported from the non-ciliated alveoli to the ciliated airways. Similarly, particles deposited on the ciliated mucus membranes of the nose are propelled toward the pharynx. There, mucus, cells, and debris coming from the nasal cavities and the lungs meet, mix with salivary secretions, and enter the gastrointestinal tract after being swallowed. Since the particles are removed with half-times of minutes to hours, there is little time for solubilization of slowly dissolving materials. In contrast, particles deposited in the non-ciliated compartments have much longer residence times and hence, there, small differences in in vivo solubility can have great significance.
- 2. A number of factors can affect the speed of mucus flow. They may be divided into two categories: those affecting the cilia themselves and those affecting the properties of the mucus. The following aspects of ciliary action may be affected: the number of strokes per minute, the amplitude of each stroke, the time course and form of each stroke, the length of the cilia, the ratio of ciliated to non-ciliated areas, and the susceptibility of the cilia to intrinsic and extrinsic agents that modify their rate and quality of motion. The characteristics of the mucus may become critically important. The thickness of the mucus layer and its rheological properties may undergo wide variations. Typical mucus carpet flow rates in the major airways are 5-10 mm/min.

B. Non-Ciliated Regions

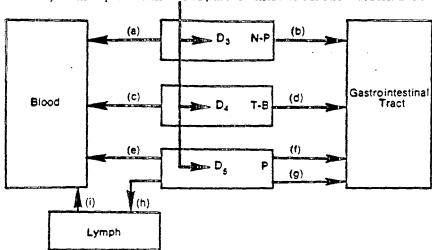
- 1. Particles deposited in the non-ciliated portion of the lungs are either moved toward the ciliated region, primarily within alveolar macrophages, or they enter the alveolar wall and accumulate in connective tissue, especially lymph nodes. Particles remaining on the surface are cleared with a biological half-time estimated to be twenty-four hours in humans, while particles that have penetrated into "fixed" tissues are cleared with half-times ranging from a few days to thousands of days. Therefore, the probability of particle penetration is critical in determining the clearance of particles from the non-ciliated regions of the lungs.
- 2. Particles removed by alveolar macrophages show a variety of patterns and half-lives which are dependent upon particle number, size, shape and surface reactivity. However, generally alveolar macrophages act to decrease the probability of particle penetration, thereby aiding clearance. These free cells, ultimately derived from the hematopoietic system, play the primary role in removal of dust particles and potentially pathogenic micro-organisms from the alveoli. Most free cells containing the deposited particles eventually reach the ciliated region of the lungs and are eliminated into the pharynx and swallowed.
- 3. The digestive capacity of the pulmonary macrophage and its ample lysosomal endowment is reflected in its high content of hydrolytic enzymes. Although this clearly constitutes an important aspect of the lung's defensive posture, when kept in a chronically activated state, this

digestive capacity may serve to damage pulmonary tissues. Release of lysosomal enzymes, particularly proteases, from activated macrophages and polymorphonuclear leukocytes may be involved in the development of emphysema. Release may occur as a consequence of cell death, cell injury, or exocytosis. Other mediators released from these cells may also be involved in fibrogenesis. Since increased particle deposition acts to recruit additional macrophages and other cells, these untoward effects may be reinforced by increased dust deposition.

IV. Retention and particle excretion.

The actual amount of a substance in the respiratory tract at any time is called the retention. When the exposure is continuous, the equilibrium concentration (achieved when the clearance rate matches the deposition rate) is also the retention. Thus, the relative rate constants of deposition and clearance determine the equilibrium levels; it is the equilibrium level, or retention integrated over time, and the properties of the particle that are presumably related to the probability of a pathological response. The pathological consequences of dust retention may be a result of its allergic, irritant, carcinogenic, infective, or other properties. Continuing research focusing on the deposition and clearance of dusts and the significance of their retention is needed.

On the figure below, an example of a model of particle excretion is shown (Ref. # 5):



—Particle deposition sites and clearance processes based on ICRP lung model. Symbols are as follows: (a), uptake of material from N-P region directly into bloodstream; (b), clearance of all particulate matter from N-P region by ciliary-mucous transport; (c), absorption of material deposited on T-B surface into systemic circulation; (d), T-B clearance by ciliary-mucous action. Particles thus cleared go quantitatively to gastrointestinal tract; (e), direct absorption of material from pulmonary region into blood; (f) relatively rapid clearance of P region (in reality, coupled to ciliary-mucous transport system); (g), relatively slow clearance process, also coupled to N-P ciliary-mucous mechanism; (h), removal of matter into lymph system; and (i), secondary pathway in which particles cleared by pathway h are introduced into systemic blood. (Adapted from Task Group on Lung Dynamics')

| Pathway | | | |
|---------|---------------------------------|---|---|
| | Class D | Class W | Class Y |
| (a) | 4 min/0.50 | 4 min/0.10 | 4 min/0.01 |
| (b) | 4 min/0.50 | 4 min/0.90 | 4 min/0.99 |
| (c) | 10 min/0.50 | 10 min/0.10 | 10 min/0.01 |
| (d) | 10 min/0.50 | 10 min/0.90 | 10 min/0.99 |
| (e) | 30 min/0.80 | 90 days/0.15 | 360 days/0.05 |
| (f) | NA | 24 hr/0.40 | 24 hr/0.40 |
| (g) | NA | 90 days/0.40 | 360 days/0.40 |
| (h) | 30 min/0.20 | 90 days/0.05 | 360 days/0.15 |
| | (b) (c) (d) (e) (f) | (b) 4 min/0.50 (c) 10 min/0.50 (d) 10 min/0.50 (e) 30 min/0.80 (f) NA (g) NA | (b) 4 min/0.50 4 min/0.90 (c) 10 min/0.50 10 min/0.10 (d) 10 min/0.50 10 min/0.90 (e) 30 min/0.80 90 days/0.15 (f) NA 90 days/0.40 (h) 30 min/0.20 90 days/0.05 |

⁹ Adapted from Task Group on Lung Dynamics.⁵ If First value is biological half-time; second, regional fraction. Lymphatic clearance for class Y compounds indicates that 10% regional fraction follows 360-day biological half-time. Remaining 90% is presumed to be permanently retained in nodes and subject only to radioactive decay.

BIBLIOGRAPHY

- I. Aerosol Deposition and Clearance in the Respiratory Tract
- 1. Brain, J.D., and P.A. Valberg. Models of lung retention based on the report of the ICRP Task Group. *Arch. Environ. Health* 28:1-11, 1974.
- 2. Davies, C.N. Deposition of particles in human lungs as a function of particle size and breathing pattern, an empirical model. In: Walton, W.H. (ed), *Inhaled Particles V.* Oxford: Pergamon Press, pp. 119-135,1982.
- 3. Churg, A. and F.H.Y. Green, eds. *Pathology of Occupational Lung Disease* Igaku-Shoin, New York, 1988.
- 4. Hatch, T. F., and P. Gross. Pulmonary Deposition and Retention of Inhaled Aerosols. Academic Press, New York. 1964.
- 5. Morrow, P. E., Chairman, Task Group on Lung Dynamics. Deposition and retention models for internal dosimetry of the human respiratory tract. *Health Phys.* 12:173-207, 1966.
- 6. Lippmann, M., D. B. Yeates, and R. E. Albert. 1980. Deposition, retention and clearance of inhaled particles. *Br. J. Ind. Med.* 37:337-362.
- 7. Valberg, P.A. Determination of Retained Lung Dose *Handbook of Experimental Pharmacology, Vol.* 75. (H.P. Witschi and J.D. Brain, eds.) Springer-Verlag, Berlin, 1985, pp. 57-91.
- 8. Valberg, P.A., J.D. Brain, S.L. Sneddon, and S.R.LeMott. Breathing patterns influence aerosol deposition sites in excised dog lungs. *J. Appl. Physiol.: Respir. Environ. Exercise Physiol.* 53:824-837, 1982.
- 9. Valberg, P.A., R.K. Wolff and J.L. Mauderly. Redistribution of retained particles: Effect of hyperpnea. *Am. Rev. Respir. Dis.* 131: 273-280, 1985.
- 10. Wolff, R. K. 1986. Effects of airborne pollutants on mucociliary clearance. *Env. Health Persepc.* 66:223-237.

II. Pulmonary Macrophages

- 11. Bowden, D. H. 1987. Macrophages, dust, and pulmonary diseases. Exp. Lung Res. 12:89-107.
- 12. Brain, J. D. 1985. Physiology and pathophysiology of pulmonary macrophages. *In:* The Reticuloendothelial System. Reichard, S.M. and J. Filkins, editors. Plenum, New York. 315-337.
- 13. Brain, J. D., and G. C. Corkery. The effect of increased particles on the endocytosis of radiocolloids by pulmonary macrophages in vivo: competitive and toxic effects. In: *Inhaled Particles and Vapours*, *IV*. W.H. Walton, Ed., Unwin Brothers, London. pp. 551-564, 1977.
- 14. Brain, J. D., J. J. Godleski, and S. P. Sorokin. Quantification, origin, and fate of pulmonary macrophages. In: *Respiratory Defense Mechanisms*, *Vol. 5.* J.D. Brain, D.F. Proctor and L. Reid, Eds., Marcel Dekker, New York. pp. 849-885, 1977.
- 15. Carr, I. The Macrophage: A Review of Ultrastructure and Function. Academic Press, New York. 1973.
- 16. Fels, A. O. S., and Z. A. Cohn. 1986. The alveolar macrophage. J. Appl. Physiol. 60:353-369.
- 17. Green, G. M. Lung defense mechanisms. Medical Clinics of North America 57:547-562, 1973.

- 18. Hocking, W.G., and D.W. Golde. The pulmonary-alveolar macrophage I. New Eng. J. Med. 301:580-587, 1980.
- 19. Hocking, W.G., and D.W. Golde. The pulmonary-alveolar macrophage II. New Eng. J. Med. 301:639-645, 1980.
- 20. Keller, H. U., M. W. Hess, and H. Cottier. Physiology of chemotaxis and random motility. Seminars in Hematology 12:47-57, 1975.
- 21. Morrow, P. E. 1988. Possible mechanisms to explain dust overloading of the lungs. Fund. Appl. Toxicol. 10:369-384.
- Sanders, C.L., Schneider, R.P., Dagle, G.E., and Ragan, H.A. (eds.). Pulmonary macrophage and epithelial cells. Proceedings of the 16th Annual Hanford Biology Symposium Richland, Washington, September 27-29,1976. Washington: Technical Information Center, Energy Research and Development Administration.
- Sanders, C.L., Cross, F.T., Dagle, G.E., Mahaffey, J.A. (eds.). Pulmonary toxicology of respirable particles. Proceedings of the 19th Annual Hanford Biology Symposium Richland, Washington, October 22-24, 1979. Washington: Technical Information Center, Energy Research and Development Administration.
- 24. Sorokin, S. P., and J. D. Brain. Pathways of clearance in mouse lungs exposed to iron oxide aerosols. Anat. Rec. 181:581-625, 1975.
- 25. Sorokin, S.P. Phagocytes in the lungs: Incidence, general behavior, and phylogeny. In: *Respiratory Defense Mechanisms*, Vol. 5. J.D. Brain, D.F. Proctor, and L. Reid, Eds., Marcel Dekker, New York. pp. 711-848, 1977.
- 26. Valberg, P.A., Chen, B.H., and Brain, J.D. Endocytosis of colloidal gold by pulmonary macrophages. Expt. Cell Res. 141: 1-14, 1982.
- 27. Valberg, P.A. Magnetometry of ingested particles in pulmonary macrophages. *Science* 224: 513-516, 1984.
- 28. Valberg, P.A. and Albertini, D.F. Cytoplasmic Motions, Rheology, and Structure Probed by a Novel Magnetic-Particle Method. *J. Cell Biol.* 101: 130-140, 1985.
- 29. VanFurth, R., ed. Mononuclear Phagocytes (2 vols.). The Hague: Martinus Nijhoff Publishers, 1980.
- 30. VanFurth, R., ed. *Mononuclear Phagocytes in Immunity, Infection, and Pathology*. Blackwell Scientific Publications, London. 1975.

- III. Bactericidal Activity of the Lungs and Phagocytic Mechanisms
- 31. Badwey, J. A., and M. L. Karnovsky. 1980. Active oxygen species and the functions of phagocytic leukocytes. *Ann. Rev. Biochem.* **49:**695-726.
- 32. Goldstein, E. Hydrolytic enzymes of alveolar macrophages *Reviews of Infectious Diseases*. 5: 1078-1092, 1983.
- 33. Green, G. M., and E. H. Kass. Role of alveolar macrophage in clearance of bacteria from the lung. J. Exp. Med. 119:617-622, 1964.
- 34. Kavet, R.I. and Brain, J.D. Methods to Quantify Endocytosis: A Review. J. Reticuloendothelial Soc. 21:201-221, 1980.
- 35. Klebanoff, S. J. 1980. Oxygen metabolism and the toxic properties of phagocytes. *Ann. Int. Med.* **93:**480-489.
- 36. Silverstein, S.C., R.M. Steinman, and Z.A. Cohn. Endocytosis. Ann. Rev. Biochem. 46:669-722, 1977.
- 37. Steinman, R.M., I.S. Mellman, W.A. Muller, and Z.A. Cohn. Endocytosis and the recycling of plasma membrane. *J. Cell Bio.* 96: 1-27, 1983.
- 38. Stossel, T. P. Phagocytosis. New Eng. J. Med. 290:717, 774, 833, 1974.
- 39. Winkelstein, J.A., and R.H. Drachman. Phagocytosis: the normal process and its clinically significant abnormalities. *Pediatrics Clinics of North America* 21:551-565, 1974.

IV. General Sources

- 40. Beck, B.D., E.J. Clabrese, and P.D. Anderson. The use of toxicology in the regulatory process. *Principles and Methods of Toxicology, 2nd Edition.* (A.W. Hayes, Editor), Raven Press Ltd., New York, pp. 1-28, 1989.
- 41. Brain, J.D., D.F. Proctor, and L. Reid, Eds. Respiratory Defense Mechanisms, Vol. 5. Marcel Dekker, New York. 1216 pages, 1977.
- 42. Cohen, A.B., and W.M. Gold. Defense mechanisms of the lungs. *Annual Reviews of Physiology* 37:325-350, 1975.
- 43. Lee, D.H.K, H.L. Falk, and S.D. Murphy (eds). Reactions to Environmental Agents. Section 9 of Handbook of Physiology (S.R.Geiger, Executive Editor). American Physiological Society, Bethesda, Maryland, 1977.
- 44. West, J.B. Respiratory Physiology. Baltimore: Williams and Wilkins, 1979.

Table 1

ANATOMY OF EPITHELIAL BARRIERS

| Interface with Environment | Area (m²) | Thickness from Environment-to-Blood (µm) | Organ Weight (kg) | | |
|-------------------------------|--------------|--|----------------------|--|--|
| skin | 1.8 | 100-1000 | 12 | | |
| gastrointestinal | 200 | 8-12 | 7 | | |
| lungs | 140 | 0.2-0.4 | 0.8 | | |

Table 2
FUNCTION OF EPITHELIAL BARRIERS

| Interface with Environment | Basal Blood Flow (liter/min) | Cell Turnover (days) | Basal Exposure Rate |
|-------------------------------|---------------------------------|-------------------------|------------------------|
| skin | 0.5 | 12 | variable |
| gastrointestinal | 1.4 | 3 | 2 kg/day |
| lungs | 5.8 | 28 | 24 kg air/day |

Table 3

Browninan diffusion (root-mean-square) in 1 second compared with distance fallen in 1 second for unit density particles of different diameter †

| | Particle Diameter (µm) | Diffusion in 1 second (µm) | Distance Fallen in 1 second (µm) |
|-------------------------|---------------------------|----------------------------------|--|
| Settling greater in 1 s | 50 | 1.7 | 70,000 |
| | 20 | 2.7 | 11,500 |
| | 10 | 3.8 | 2,900 |
| | 5 | 5.5 | 740 |
| | 2 | 8.8 | 125 |
| | 1 | 13.0 | 33 |
| Diffusion greater in 1s | 0.5 | 20 | 9.5 |
| | 0.2 | 37 | 2.1 |
| | 0.1 | 64 | 0.81 |
| | 0.05 | 120 | 0.35 |
| | 0.02 | 290 | 0.013 |
| | 0.01 | 570 | 0.0063 |

^{*} Temperature, 37°C; gas viscosity 1.9×10^{-5} Pa-s; appropriate correction factors applied for motion outside the range of validity of Stoke's Law.

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The Respiratory Tract as a Portal of Entry for Toxic Particles

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Our ambient, external environment poses a constant threat to the life and health of cells that make up our body. The external environment is cold, dry, septic (putrefactive), toxic, and widely variable in chemical composition, salinity, and acidity. In contrast, our internal environment is represented by the fluid that surrounds our cells and keeps them alive. The internal environment is warm, wet, sterile, and nontoxic, and has an ionic-chemical composition that is closely regulated by homeostatic processes. The internal and external environments confront each other across epithelial barriers, comprising primarily the skin, the gastrointestinal tract, and the respiratory system. These barriers are differentially susceptible to attack, and the route by which a toxic insult enters the body can determine its effectiveness. Pure water in the lungs or pure air in the circulating blood are more life threatening than polluted air in the lungs or alcohol in the circulation.

The purpose of this chapter is to contrast the three major portals of entry, with particular emphasis on the lungs and the entry of inhaled particles. Our lung surfaces, due to their primary function of gas exchange, come into intimate contact with irritating gases and airborne particles. The same thinness and extensive area that qualify this air-blood barrier for the rapid exchange of oxygen and carbon dioxide reduce its effectiveness as a barrier to inhaled microorganisms, toxic particles, and noxious gases [1]. Inhalation of these agents may initiate or aggravate lung disease. In order to assess adequately the risks of inhaled-particle exposure, we need to characterize the fate of particles entering the respiratory tract.

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ANATOMICAL CHARACTERISTICS

Some of the anatomical differences between the skin, gastrointenstinal tract, and the respiratory system are summarized in Table 1. The skin envelops the outside of the body and is a mechanically strong epithelium, with many complex specializations such as hairs, nails, pigmentation, and glands. The total weight of skin (dermis plus epidermis) is about 12 kg in a 70 kg human. The gastrointestinal tract is a long tube topologically continuous with the skin at both ends and exhibits absorptive and surface area specializations along its length; its total weight is about 7 kg. The respiratory system begins at the mouth as a single pathway that repetitively bifurcates into a complex branched system of tubes, which terminate in blind-ended sacs, the alveoli. The lungs, being air-filled, contribute only about 1% to body weight, or 0.8 kg [2]. The skin, gastrointestinal tract, and lungs have important elastic and smooth muscle components, but the lungs are unique in that an important function, that is, expiration, is crucially dependent on its elastic properties alone.

In the context of route-to-route extrapolation, the significant anatomical characteristics of these barriers are their surface area and thickness (Table 1). The barrier function of the skin is evident with its much smaller surface area (1.8 m²) and considerably greater thickness (100 to 1000 µm) when compared to the other two epithelial barriers. In the gastrointestinal tract, surface area is not limited to that of a 10-m long tube, but is augmented by intestinal folds, villi, and microvilli, to achieve a surface area equivalent to about a doubles tennis court (200 m²). Most of the gastrointestinal tract absorptive epithelium is simple columnar so that the distance from lumen to blood is approximately 8 to 12 µm. In the lungs, a large surface area (a singles tennis court, 140 m²) is achieved by repetitive branching (about 16 generations) so that the initial tube, the trachea, is connected to 300 million alveoli [3]. The gas-exchange epithelium is simple squamous, giving a very short distance (0.2 to 0.4 µm) between the air and blood.

Table 1. Anatomy of epithelial barriers.

| Interface with Environment | Area (m²) | Thickness from Environment to Blood (µm) | Organ Weight (kg) |
|-------------------------------|--------------|---|----------------------|
| Skin | 1.8 | 100-1000 | 12 |
| Gastrointestinal | 200 | 8-12 | 7 |
| Lungs | 140 | 0.2-0.4 | 8.0 |

FUNCTIONAL DIFFERENCES

The functions of the skin are primarily those of a barrier, that is, to prevent entry of microorganisms and other environmental agents and to prevent water and heat loss. The gastrointestinal tract has absorptive capacities that are both active (i.e., can work against a concentration gradient) and well regulated (i.e., degree of absorption can be modified). In addition, bacteria that thrive in the gastrointestinal tract are prevented from entering the circulation. The respiratory epithelium exchanges oxygen and carbon dioxide, both of which diffuse passively down concentration gradients. The air-liquid interface of the lungs is an additional unique property of this barrier. Like the other two barriers, inhaled pathogens must be prevented from reaching the blood. However, the lungs also have other "functions", namely, vocalization, coughing, sneezing, and straining in defecation [4].

Some of the functional characteristics relevant to route-to-route extrapolation are shown in Table 2. The quantity of exposure is dramatically different among the several routes. On a daily basis, the mass of air we inhale (approximately 24 kg) exceeds by far the mass of material entering daily into our gastrointestinal tract (approximately 2 kg). There are also important blood flow differences. The lungs always receive the total cardiac output. The gastrointestinal tract and the skin receive only a (variable) fraction of total blood flow. At rest, the gastrointestinal tract and skin receive about 25 and 10% of cadiac output, respectively. During exercise total cardiac output may triple, but the gastrointestinal tract percentage falls to 3%, and the skin percentage rises slightly to about 12% [2]. Flow in the gastrointestinal tract is generally unidirectional, proceeding from one orifice to the other. Flow in the lungs is tidal; that is, airflow reverses on a periodic basis, and air moves in and out of a single orifice.

The time scale for throughput is another relevant consideration when assessing functional differences. Breathing is an act that must be continuous on a minute-by-minute basis, whereas the intervals

Table 2. Epithelial barrier dynamics.

| Interface with Environment | Basal Blood Flow (L/min) | Cell Turnover (days) | Basal Exposure Rate |
|-------------------------------|-----------------------------|-------------------------|---------------------|
| Skin | 0.5 | 12 | variable |
| Gastrointestinal | 1.4 | 3 | 2 kg/day |
| Lungs | 5.8 | 28 | 24 kg air/day |

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between food and water intake can be much longer. This means that our choice of the air we breathe is less voluntary than of the food and water that we ingest. In fact, world-record breath-holding time (13 min, 42.5 sec) is much shorter than world-record fast duration (382 days) [5]. Finally, the dynamic range of breathing between sleep and heavy exercise can cover a factor of about 30 in minute ventilation, so that delivery of potentially polluted air to respiratory surfaces is dependent on state of exercise [4].

INHALATION OF AIRBORNE PARTICLES

One hundred years ago, in 1882, John Tyndall published his essay "Floating-Matter of the Air in Relation to Putrefaction and Infection." Using the light-scattering instrument that bears his name, Tyndall showed that the air we exhale is less dusty than the air we inhale, thus demonstrating that the lungs act as a filter for airborne particles. The three main factors acting to bring inhaled particles in contact with lung surfaces are (1) settling under the influence of gravity; (2) particle inertia, which carries particles straight when airflow turns; and (3) particle Brownian diffusion from random gas collisions [6, 7]. The relative effect of particle settling versus diffusion can be appreciated by examining Table 3, which shows the relative amount of distance traveled by unit density particles of different size. For example, in 1 sec a 2-µm diameter particle diffuses a root-mean square distance of 8.8 µm, whereas during the same time it falls 125 µm, so that settling is the dominant influence in moving the particle toward lung surfaces. On the other hand, a particle 0.1-µm diameter diffuses a distance of 64 μm in 1 sec, but falls only 0.81 μm; thus Brownian motion is a more important deposition mechanism [8].

In addition to particle characteristics, aerodynamics of respiration and anatomy of the airspaces influence particle deposition. The nose acts as a prefilter, capturing very large particles (5 to 10 µm). Large particles are also susceptible to inertial impaction in the airways where flow is high and air streamlines change directions frequently. Particles that penetrate to the small bronchiolar and alveolar region can be collected rapidly by settling and diffusion. Total collection efficiency for the lung is lowest in the particle size range around 0.5 µm, because these particles do not settle very rapidly, yet they are too large to diffuse effectively (cf. Table 3, the sum of Brownian displacement in 1 sec plus distance fallen in 1 sec is least for 0.5-µm particles). Aerodynamics of respiration also influences particle delivery and deposition. Minute ventilation can vary from a low of about 5 L/min at rest to a high of about 140 L/min, which is maximum voluntary ventilation. Delivery of particles to the lungs varies in direct proportion

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Table 3. Brownian diffusion (root-mean-square) in 1 sec compared with distance fallen in 1 sec for unit density particles of different diameter.a

| | Particle Diameter (µm) | Diffusion in 1 sec (µm) | Distance Fallen in 1 sec (µm) |
|----------------------------|---------------------------|----------------------------|----------------------------------|
| Settling greater in 1 sec | 50 | 1.7 | 70,000 |
| | 20 | 2.7 | 11,500 |
| | 10 | 3.8 | 2,900 |
| | 5 | 5.5 | 740 |
| | 2 | 8.8 | 125 |
| | 1 | 13.0 | 33 |
| Diffusion greater in 1 sec | 0.5 | 20 | 9.5 |
| | 0.2 | 37 | 2.1 |
| 1 | 0.1 | 64 | 0.81 |
| | 0.05 | 120 | 0.35 |
| | 0.02 | 290 | 0.013 |
| | 0.01 | 570 | 0.0063 |

a Temperature: 37 °C; gas viscosity: 1.9 x 10-5 Pa-s; appropriate correction factors are applied for motion outside the range of validity of Stokes Law.

to minute ventilation. The ventilatory pattern can modify deposition. Slow, deep breathing delivers more particles distally than rapid, shallow breathing. Total deposition is greater with slow, deep breathing, and is more uniformly distributed than with rapid, shallow breathing [9, 10].

Dose to the respiratory tract from inhaled particles is proportional to particle retention, and integrated particle retention is derived from the balance of the two processes: deposition and clearance. The mechanics of these processes are presently not understood well enough to calculate retention with confidence from a priori structure and Comparison of experimental morphometric, function data. physiologic, and cellular characteristics of the respiratory tract among different mammalian species allows some insight into mechanisms that may be important when using animal data to evaluate the human respiratory tract as a route of toxic particle entry [11]. Examples of such parameters include ventilation per unit surface area, average lung airspace size, mucociliary clearance rate, and pulmonary macrophage number per unit lung surface area (Table 4) [12, 13].

TABLE 4. Lung and alveolar macrophage parameters as they may relate to *in vivo* particle uptake.

| | | Mammalian Species | | | | | | | |
|--|---------|-------------------|---------|---------------|---------|--------|------------------------------------|--|--|
| | Mouse | Hamster | Rat | Guinea Pig | Rabbit | Dog | Human | | |
| Avg. body wt. (g) | 42 | 122 | 380 | 430 | 2600 | 16,000 | 74,000 | | |
| V _L (mL) | 1.45 | 3.9 | 10.9 | 13 | 112 | 1320 | 4340 | | |
| S _A (m ²) | 0.125 | 0.28 | 0.66 | 0.91 | 3.3 | 52 | 143 | | |
| Alveolar diam. (μm) | 47 | 60 | 70 | 65 | 88 | 126 | 219 | | |
| Calculated # of alveoli (millions) | 18 | 25 | 43 ^ | 69 | 135 | 1040 | 950 | | |
| Average # of lavagable AMs per animal (millions)a | 0.67 | 4.7 | 4.9 | 3.2 | 30 | 3800 . | 6400 | | |
| Calculated AMs per alveolus | 0.037 | 0.19 | 0.11 | 0.046 | 0.22 | 3.7 | 6.8 | | |
| Area patrolled by each AM (µm²) | 190,000 | 60,000 | 140,000 | 280,000 | 110,000 | 13,400 | 22,000 | | |
| In vivo particle uptake by AM (T ₁ , hours) | 7.1 | 0.8 | 4.2 | | 3.2 | coeff | elation icient area = .99 | | |

a AM = Alveolar macrophage

DEFENSE MECHANISMS FOR THE THREE ROUTES

Defense against penetration of the skin relies primarily on the mechanical strength of the cornified layer skin in addition to the underlying stratified squamous cells, which are linked to each other by tight junctions. The sebaceous glands, which secrete an oily/waxy layer coating the skin, are an additional line of defense. However, even though the skin is resistant to aqueous toxins, ionic, organic, and lipid-soluble agents can penetrate. Carbon tetrachloride (CCl₄), organophosphate pesticides, and coal tar pitch volatiles (CPTV) are examples of toxic substances that can cross the skin and cause deleterious effects in the liver (CCl₄) or nervous system (organophosphates), or can cause skin (scrotal) cancer (CTPV). Finally, skin cells slough off with a time constant of 12 days so that toxins in the outer layers can be removed [14].

The gastrointestinal tract has several first-line defenses: vomiting, the acidic environment of the stomach, and the proteolytic environment of the small intestine. The gut epithelium comprises metabolically active columnar cells, and uptake from the gut is selective to some degree. Furthermore, the constant throughput of the gastrointestinal tract assures that substances will remain in contact with the epithelium for only a limited amount of time. The turnover time of the gut epithelium is very rapid (about three days), and damaged, leaky cells are rapidly sloughed off and replaced by vigorous counterparts. Finally, because blood outflow from the gastrointestinal tract goes directly to the liver, toxins can be potentially deactivated before reaching the general circulation.

The first line of defense of the respiratory tract are the cough and sneeze reflexes. In the nose, fine hairs filter out large particles. In the major airways, a mucus coating serves two defense functions. First, if particles settle on the mucus, the mouthward transport driven by the underlying cilia ensures that the particles are moved out of the lung and into the gastrointestinal tract, where they can be eliminated from the body. Second, for toxic, reactive gases, such as ozone, the mucus forms a protective layer that reacts with these agents and thereby protects the epithelium underneath. Surfactant in the alveoli may serve this role to a lesser degree due to its limited thickness. The alveolar epithelial cells provide less protection than those in the gut because they are thinner and less metabolically active. Moreover, the turnover time of the alveolar epithelium is about 28 days so that damage is not as easily repaired [15, 16].

The alveolar surfaces are, however, protected by the pulmonary macrophage, a wandering, phagocytic cell that has remarkable properties in terms of recognizing, ingesting, and deactivating bacteria and particles [16, 17]. The phagocytic process not only exposes the particles (or pathogens) to lysosomal proteolytic enzymes, but also provides a transport mechanism whereby particles can leave the lungs. That is, an inhaled and deposited particle may of itself be completely immobile on the lung surfaces and thus fail to leave the lung over long periods of time. However, ingestion by a macrophage imparts the cell's mobility to the particle, and since the cell may ultimately translocate to the mucus carpet, this route of mechanical clearance now becomes available to the particle. Ingestion by the macrophage also helps prevent particle penetration through the epithelium into interstitial and lymphatic compartments where clearance likely proceeds by solubilization alone.

The time scales of particle clearance are dramatically different between lung and gastrointestinal tract. Due to the continuous motility of the gastrointestinal contents, ingested material generally passes out of the body in 24 h. Although this time constant is similar to the time needed for material caught in the mucus to be transported out of the lungs, clearance of insoluble particles from the alveolar lung region takes much longer, with half times in the range of six months to several years [18, 19].

The ability of the lung macrophage to clear insoluble particles depends on several factors: (1) the intrinsic ability of the macrophage to phagocytize particles, (2) the motile ability of the macrophage (which may be inhibited by increasing particle load) [20], (3) the amount of lung surface area patrolled by each macrophage, and (4) the average distance between the site of particle phagocytosis and the most distal point to which the mucociliary escalator extends. Intrinsic differences in phagocytic or motile ability among macrophages of different species have not been described, but if the number of macrophages lavaged from the lungs is an indication of the quantity of resident alveolar macrophages, then it would appear that there are systematic differences between the number of macrophages per alveolus and average lung surface area per lung macrophage. These comparisons are shown on Table 4. The number of lung macrophages recovered can be increased by "vigorous" lavage, but since this procedure has been applied extensively only in the rat, the figures used for lavagable alveolar macrophages apply to a more widely-used, gentler procedure. The calculations suggest that macrophages from the mouse and guinea pig must cover a larger surface area and phagocytosis of randomly deposited particles probably proceeds more slowly. In the hamster, dog, and human there are more macrophages per unit surface area, and thus, particles are likely reached sooner. For those species in which in vivo colloidal gold particle uptake has been studied, there is good correlation between halftime of gold particle uptake and the area patrolled per macrophage.

SUMMARY

With respect to the integrity of the various epithelial barriers, the respiratory tract seems to be the most susceptible to being breached. Various anatomical and functional characteristics of the lungs contribute to their being a major reute of entry of pollutants into the body. The surface area of the lungs is comparable to the gastrointestinal tract, but the thickness of the epithelium is considerably less. The respiratory system has the greatest total mass of environmental media presented to it each day. The blood circulation through the respiratory system is greater than that of the gastrointestinal tract. Clearance of distally deposited material from the

respiratory system is more complex and with a longer time constant than in the case of the gut. Finally, repair of epithelial injury is likely not as rapid as in the gut. In light of these considerations, it is surprising that legislation which seeks to protect us from carcinogens (U.S. Food and Drug Administration, Delaney Amendment) is more concerned about the presence of carcinogens in food products than carcinogens present in inhaled consumer products [21].

REFERENCES

- E.R. Weibel, The Pathway for Oxygen, Structure, and Function in the Mammalian Respiratory System (Harvard University Press, Cambridge, MA 1984).
- A.J. Vander, J.H. Sherman, and D.S. Luciano, Human Physiology (McGraw-Hill, New York, 1990).
- P. Gehr, M. Bachofen, and E.R. Weibel, The normal human lung: Ultrastructure and morphometric estimation of diffusion capacity, Respir. Physiol. <u>32</u>:121-140 (1978).
- J.B. West, Respiratory Physiology The Essentials, 3rd ed. (Williams and Wilkins, Baltimore 1979).
- D. McFarlan, N.D. McWhirter, D.A. Boehm, C. Smith, J. Benagh, G. Jones, and R. Obojski, Guinness Book of World Records (Bantam Books, New York 1990) pp. 33-36.
- M. Lippmann, D.B. Yeates, and R.E. Albert, Deposition, retention, and clearance of inhaled particles, Br. J. Ind. Med. <u>37</u>, 337-362 (1980).
- P.E. Morrow, Deposition and retention models for internal dosimetry of the human respiratory tract, Health Phys. <u>12</u>, 173-207 (1966).
- 8. P.A. Valberg, Determination of Retained Lung Dose in: Handbook of Experimental Pharmacology, Vol. 75s, H.P. Witschi and J.D. Brain, eds. (Springer-Verlag, Berlin 1985) pp. 57-91.
- C.N. Davies, Deposition of particles in human lungs as a function of particle size and breathing pattern, an empirical model in: Inhaled Particles V., W.H. Walton, ed. (Pergamon Press, Oxford 1982) pp. 119-135.
- P.A. Valberg, J.D. Brain, S.L. Sneddon, and S.R.LeMott, Breathing patterns influence aerosol deposition sites in excised dog lungs, J. Appl. Physiol.: Respir. Environ. Exercise Physiol. <u>53</u>, 824-837 (1982).
- P. Gehr, D.K. Mwangi, A. Ammann, G.M.O. Maloiy, C.R. Taylor, and E.R. Weibel, Design of the mammalian respiratory system, V. Respir. Physiol. <u>44</u>:61-86 (1981).

- 12. P.A. Valberg and J.D. Blanchard, Pulmonary macrophage origin, endocytic function, and fate in: The Normal Lung: Comparative Pulmonary Biology, R.B. Schlesinger, ed. (Telford Press, Caldwell, NJ [in press]).
- 13. P.A. Valberg, B.H. Chen, and J.D. Brain, Endocytosis of colloidal gold by pulmonary macrophages, Expt. Cell Res. 141, 1-14 (1982).
- Reactions to Environmental Agents, Section 9 of Handbook of Physiology, S.R. Geiger, D.H.K. Lee, H.L. Falk, and S.D. Murphy, eds. (American Physiological Society, Bethesda, MD 1977).
- J.D. Crapo, B.E. Barry, P. Gehr, M. Bachofen, and E.R. Weibel, Cell number and cell characteristics of the normal human lung, Am. Rev. Respir. Dis. <u>125</u>:332-337 (1982).
- S.P. Sorokin, Phagocytes in the lungs: Incidence, general behavior, and phylogeny in: Respiratory Defense Mechanisms, Vol. 5.
 J.D. Brain, D.F. Proctor, and L. Reid, eds. (Marcel Dekker, New York 1977) pp. 711-848.
- 17. S.P. Sorokin, and J.D. Brain, Pathways of clearance in mouse lungs exposed to iron oxide aerosols, Anat. Rec. 181, 581-625 (1975).
- 18. D.H. Bowden, Macrophages, dust, and pulmonary diseases, Exp. Lung Res. 12, 89-107 (1987).
- A.O.S. Fels, and Z.A. Cohn, The alveolar macrophage, J. Appl. Physiol. <u>60</u>, 353-369 (1986).
- 20. P.E. Morrow, Possible mechanisms to explain dust overloading of the lungs, Fund. Appl. Toxicol. <u>10</u>, 369-384 (1988).
- 21. B.D. Beck, E.J. Clabrese, and P.D. Anderson, The use of toxicology in the regulatory process in: Principles and Methods of Toxicology, 2nd Edition, A.W. Hayes, ed. (Raven Press Ltd., New York 1989) pp. 1-28.

Avenues of Exposure -- Indoors & Outdoors

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Limitations to the Use of Employee Exposure Data on Air Contaminants in Epidemiologic Studies

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Summary. The bias in the estimation of uptake of substances in the human body from exposure data gathered from ordinary workplace check-ups is discussed. It is concluded that most exposure is probably overrated. This means that exposure limits based on these premises will tend to be too high. To counteract this bias in the future, filed exposure data should be accompanied with information on a number of circumstances which prevailed at the sampling.

Key words: Bias - Exposure data - Air contaminants - Work sites - Permissible exposure limits

Introduction

The purpose of an epidemiologic investigation is to establish a causal association between categories of events occurring in a group of persons; one category being, for example a disease in a certain proportion of the group and another category being an attribute or experience in a certain proportion of the group [21]. This attribute or experience in occupational health will often be an exposure to a known chemical or physical factor. The definition of noneffect levels of these factors or even the substantiation of dose-response or dose-effect relationships is of special interest for the purpose of setting or revising exposure limits [16]. This ambition as goal unfortunately is often hampered by the inadequacy of exposure data.

The concept of exposure of an employee to a substance in the work environment may denote at least two things. It may indicate the dose of the substance absorbed in the body. It may also merely indicate the presence of the employee in an environment in which there is a more or less well determined concentration of the substance, from which an uptake of the substance is deduced. The purpose of the following inquiry is to discuss the bias in the estimated uptake. Random error in concentration determinations, although important as such, is considered only briefly in this context.

Exposure measurements may be performed either in order to check if the priving ment complies with exposure limits or, at least in theory, in order to estimate the uptake of a substance for the purpose of epidemiologic studies. It is important to separate these two goals, since the outcome of measurements with one or the other purpose will be quite different.

Most epidemiologic studies are retrospective. If a prospective investigation is considered, it is probably also justified to control the exposure, which will entirely change the premises of the investigation [16]. Consequently most epidemiologic studies are reduced to using data from measurements already made, and made for other purposes. Hence it is important to judge the relevance of the few data which may be found in the best possible way. The following factors and circumstances may affect the bias of estimated uptake deduced from exposure data: (a) the intention of the measurement, (b) the methods used and (c) the investigation strategy. These factors affect the representativeness of the exposure data. Additional factors affecting the uptake but not the concentration of contaminants in the air must also be considered. Such factors are (d) part-time exposure, (e) the use of respirators, (f) personnel rotation, (g) unfavourable distribution of exposure periods over time and (h) unusually hard work increasing the ventilation of the exposed individual.

2. Methods

2.1 Sampling of Air Contaminants

The measurement of exposure to air contaminants may be performed by analysing their concentration and variation with time in the inhaled air of the exposed employee. This can be accomplished by sampling close to the nose of the employee. This has been a regular practice rsince the introduction of portable equipment including battery driven pumps in 1960 [25]. It is also possible to estimate exposure from data on the concentrations in various places or "zones" where the employee is present [10] or from exposure data with regard to various occupational titles or uniform task classes to which the employee belongs [11, 12, 32].

2.2 Investigation Strategies

The purpose of this section is to list and describe sampling strategies which are in current use or may have been used in the past.

- 2.2.1 No Visits "Startegy". When no visits at all are made to a work place, this "strategy" may be a well founded choice or due to lack of resources, or even ignorance.
- 2.2.2 Inspection. At its best an inspection is a qualified evaluation based upon surveying a place of work and a work operation, possibly combined with inference from earlier measurements at the same place of work or what are supposed to be similar places of work. Actual measurements may occasionally be performed at the inspection, e.g. by detection tubes or other direct reading instruments. When notations have been made regarding reactions to the environment, e.g. smell of a substance or acute reactions of the employees as irritation, lachrymation or even fainting, conclusions as to the level of exposure may be drawn. The few data generated in an inspection are unlikely to be representative. The samples may refer to the general work room atmosphere or to the "worst case" without any reference in the records.
- 2.2.3 Identification. This indicates sampling and analysis with the purpose of identifying unknown substances in the air. The samples may be taken, e.g. by a "high volume sampler" in a suitable position of the premises investigated or by other means depending on how the

determinations are to be performed. Identification of unknown substances are meant to be just qualitative and any noted concentrations are not likely to represent normal conditions. The desire to collect enough material for a determination will probably lead to a positive bias, in such data.

- 2.2.4 Finding "Worst Cases". Random samples (grab samples) are taken during minutes or longer periods depending on the sensitivity of the analytical methods in the vicinity of operations and during phases of operations where high exposure is expected. The purpose is to get a measurement relevant to the "worst possible case" and also to check compliance with ceiling standards. "Whorst cases" are by definition not representative. If the results are applied to other groups within the same industry, the bias will be positive.
- 2.2.5 Monitoring of Time Weighted Average Concentrations. The goal is to measure the daily average exposure of selected employees during normal production and to check compliance with exposure limits [28]. The samples may be taken as a number of short-period samples at random during a day or as full period samples [19,28]. If data are applied to other groups of employees, the bias may be positive or negative depending on how the selection was made.
- 2.2.6 Work Area Sampling. This may indicate static sampling in the work area in order to investigate the background concentration of the air contaminant there with no particular regard to the exact position of the employees in the localities. Such sampling will in itself not reveal exposure. The level of exposure has to be derived from other data as well. These data may be incomplete or entirely lacking. Since the occupational hygienist may be inclined to sample where he can get high results, while the employees avoid "hot spots" if they can, the bias may be positive.

Work area sampling may also indicate static sampling made with regard to positions of employees where an average concentration is likely. In this case, much random error in estimating individual exposure is likely, but not essentially biased.

- 2.2.7 Emission Measurement. Measurement of the emission (weight unit of contaminants per time unit) from different sources of contamination is applied in a few instances. Emission measurements say nothing about the exposure. The calculations involved in order to derive the exposure are based on several very uncertian factors, e.g. production, ventilation, air movements, and positions of employees in the localities.
- 2.2.8 Biological Sampling. When sampling and analysis of e.g. blood or urine from exposed employees is applicable, they are supposed to reflect uptake in individuals or groups in the best possible way. The relationship to exposure in the environment varies with the substance in a complicated way, however. Samples may be taken when a dangerous exposure is expected, but it is also possible that all employees of a certain trade are examined on a routine basis.

Strategy no. 2, sometimes combined with no. 3, may form the introductory phase of a planned larger exposure monitoring program. The most common of the strategies is no. 1 and then nos. 4, 5 and 8. Strategies nos. 4 and 5 may be applied separately or combined. The importance of strategy no. 6 has decreased since portable sampling equipment has been introduced, but it is still used in connection with the planning and checking up of control measures. Strategy no. 7 is unusual, especially since it is difficult to arrange for emission measurements in the normal operations of a factors. A hybrid between emission and immission measurements has been practised in a study of welders [31].

2.3 Compliance Testing

Compliance with exposure limits may be tested in different ways. While Leidel et al. [19] advocate a very precise statistically based compliance testing, others prefer qualitative reasoning, e.g. the Swedish authorities [8]. Most suggested procedures are derived from the following models.

2.3.1 Conventional Procedure. Compliance exists when the time weighted arithmetic mean is below the exposure limit. Excesses above the limit are permitted within short-term exposure

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limits [6, 8]. The short-term exposure limits will function as a limit to the acceptable range in readings when the mean is close to the exposure limit and thus limit the chance of false statements of compliance.

2.3.2 Testing of Statistical Hypothesis. Comparison with the Confidence Limits. The normal or log-normal distribution model is used to calculate the upper and lower confidence limits of the mean at some reasonable confidence level. It is suggested that the lower confidence limit be used primarily by the compliance officer to test possible noncompliance with exposure limits and that the upper confidence limit be used primarily by the employer to test possible compliance with exposure limits [19]. A shortcoming of this procedure is that the range in readings is not controlled. Therefore the power of the test should also be considered [28].

2.3.3 Overexposure Risk. The risk of overexposure on any occasion when the apparant exposure on that occasion is in compliance with the exposure limit has been calculated considering various premises [20]. It is suggested that an "action level" of half the exposure limit be used.

2.4 Decision Models

It is a fact that the eagerness with which exposure limits have been enforced has varied considerably with time and from one nation to another, as it depends among other things on the legal status of the exposure limits. The consequences of noncompliance with exposure limits therefore have been very different in different situations in the past. The decisions critical to the bias of old exposure data regard the possibility of repeating measurements and the control measures taken. If effective control measures result from a decision of noncompliance with exposure limits, the old exposure data will rapidly be rendered obsolete. If applied to future situations they will be positively biased. If measurements are repeated only when high concentrations are registered and further measurements cancelled when a single low reading is observed, negative bias is inevitable.

A detailed decisions scheme has been developed for the National Institute of Occupational Safety and Health [19]. When the exposure limit has been exceeded, the person is informed about it and control measures taken. Then new measurements are performed at regular intervals until repeated results show concentrations below the "action level". When the "action level", but not the exposure limit, is exceeded measurements are performed at regular intervals until repeated results show concentrations below the "action level". If this program is enforced the influence of chance in measurements and decisions will be minimized. The data generated will probably be representative for most exposed employees on the premises. Important to the usefulness of exposure data are also the decisions taken when random samples are far below the exposure limit. In most cases all further measurements will be cancelled when concentrations are well below the exposure limit and the number of data in such situations therefore will be very limited.

3. General Representativeness of Exposure Measurements

3.1 Distribution of Concentrations of Air Contaminants

Concentrations of samples of contaminated air usually have positively skewed distributions. It is now rather generally acknowledged that these distributions are approximately log-normal [19, 28], i.e. the logarithms of the concentrations are normally distributed [2]. As an example, the general agreement with the lognormal distribution of a large amount of concentration data in connection with welding has been confirmed [31].

The relative positions of the mean, median (= geometric mean) and mode (= most frequent value) at $e^{\mu + 12\pi^2}$, e^{μ} and $e^{\mu - n^2}$ (μ and σ being the mean and

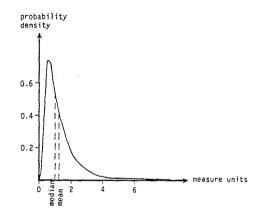


Fig. 1. Relative positions of arithmetic mean and median in the log-normal distribution

Table 1. The area on the left of the arithmetic mean under frequency curves of log-normal distributions with varying geometric standard deviation

| GSD | Area |
|-----|------|
| 1.5 | 0.58 |
| 2 | 0.64 |
| 2.5 | 0.68 |
| 3 | 0.71 |
| 3.5 | 0.73 |
| 4 | 0.76 |
| | |

-standard deviation of the logarithms of the variate) emphasize the positive skewness of the distribution, cf. Fig. 1. Some authors also refer to the geometric standard deviation, GSD= e^{σ} [19, 20]. A simple relation obtains between the quantiles of the log-normal distribution and the corresponding quantiles of a normal distribution with mean = 0 and standard deviation = 1. If v_q is the quantile of order q of the normal distribution then the q:th quantile of the log-normal distribution will be $e^{\mu + v_q - \sigma}$.

The skewness of distributions of air contaminant concentrations found in industrial operations has been investigated by Leidel et al. [20]. Also, quoting other authors, they conclude that the median category of GSD's of particulate sampling data from a great number of measurements in various branches was 1.60 to 1.69 and the median category GSD's of gas and vapour sampling data 1.50 to 1.59 [20].

The difference in intra- and interindividual variations may be exemplified with the dust exposure of 63 welders performing shielded electric arc welding on stainless steel [30]. Dust was sampled inside their face guards in the morning and in the afternoon. The GSD within days (same welder) was 1.2 and between welders 1.6 on the average.

An illustration of the consequences of the skewness is given in Table I giving the relative frequencies with which log-normal distributed observations will fall below the arithmetic mean when the GSD varies. If the distribution is normal 290 U. Ulfvarson

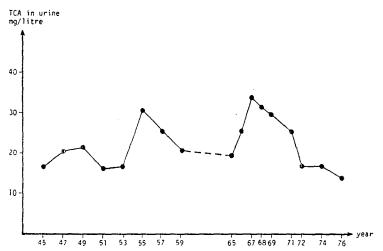


Fig. 2. Yearly geometric means of TCA in urine samples taken in health controls on employees exposed to trichlorethylene in Sweden 1945–1976

this frequency by definition is 50%. When the skewness increase the relative frequency of observations below the arithmetic mean increases, e.g. there is more than a 70% chance in random sampling of observing a single variate less than the arithmetic mean when the geometric standard deviation is 3, a high but not unusually high spread. Only if a number of observations are made, will the mean converge with the true overall mean. The importance of the arithmetic mean is obvious considering that, in full period sampling, the arithmetic mean of the period is automatically registered and that in principle the accumulated uptake of the human body is proportional to the arithmetic mean of the period under observation. This will be further discussed below.

3.2 Variations in Exposure over Long Periods

In Sweden and other industrialized countries there has been a general trend towards lower employee exposure to air contaminants in the work environment at least during the 1970's, as indicated by the continuous revisions of the exposure limits. The trend is shown in those cases where long-term series of incidences of occupational diseases or exposure measurements are available as reported for silicosis and quartz exposure [1]. As a measure of exposure to trichloroethylene, trichloroacetic acid (TCA) has been determined in urine for a long time [3]. Each year since the 1940's, hundreds of urine samples have been sent to the National Institute of Public Health, later the Institute of Occupational Health, in Sweden for analysis of TCA. The yearly geometric means of these analyses are plotted in the Fig. 2. The curve indicates a general long-term increase in the exposures on to the end of the 1960's and then a significant decrease. The yearly means of the concentrations of lead in blood samples taken in health controls in Finland during a number of years has been reported [17]. From 1969 on to 1976 there has been a steady and substantial decrease.

Table 2. Investigations in a number of representative paints factories in 1976 and 1979. Range of the sum of concentrations of solvents, each standardized with the corresponding permissible exposure limit value in common operations before and after an extensive cleaning-up program [4, 26, 29]

| Operation | Before control (1976) | After control (1979) |
|-------------------------------------|--------------------------|-------------------------|
| Charging of raw materials | 0.02-16.0 | 0.15- 0.54 |
| Pigment dispersion | 0.2 - 4.4 | 0.43- 0.78 |
| Tinting | 0.1 - 2.0 | 0.3 - 2.4 |
| Filling of cans | 0.02- 6.6 | 0.12- 1.1 |
| Cleaning of equipment with solvents | 0.5 -30.0 | 0.33-47.0 |

It is obvious that a lot of changes habe been imposed on the individual factory, e.g. as a result of measures taken to limit exposure or as a consequence of changes in the production. It is necessary to have accurate knowledge of the investigated factory or branch if exposure data is to be correctly interpreted. As an example, two surveys in the paint industry in 1976 and 1979 [4, 26, 29] are presented in the Table 2. Between these two years large-scale cleaning up operations were in progress in the whole branch. As a result the exposure to solvents decreased considerably in several types of operations. The group of persons occupied with the solvent cleaning of equipment, who were the worst exposed employees, showed no change in their conditions, however.

The conclusions of these examples is that if exposure data are generalized over a long period of time, the estimated uptake of substances will probably be considerably in error. The sign of this bias will vary depending on the long-term development of the exposure to the substance in particular and how the generalization is made.

3.3 Variations in Exposure with the Time of the Year

When there is a season effect on exposure this must obviously affect the inference from measurements during one season to other seasons. An example of effects due to the time of the year is given in the Fig. 3, showing the exposure of welders to welding fumes. Welding the same material and with the same method is performed in a rather similar way irrespective of where it is done [31]. In the figure geometric means of exposure of different welders in different enterprises working with three independent methods have been plotted against the month of the year in which the measurements were made. The differences are significant according to analyses of variance performed with the logarithms of the concentrations. A second example is given in the Fig. 4. Monthly geometric means of TCA concentrations in urine samples mentioned above show a significant seasonal effect on exposure.

An explanation of the season effect on the two entirely different exposure situations in the examples may be the changes in the general ventilation during a year. When the outdoor climate is mild in Sweden in May through August, the air exchange through windows and doors may be important, while there is a

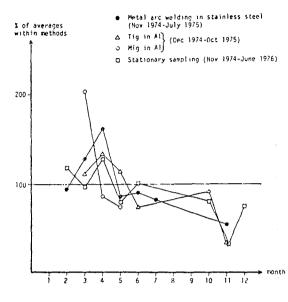


Fig. 3. The effect of the season. Geometric means of concentrations of welding fumes in the inspiration air of the welders inside the face guard and at stationary sampling places in the work rooms. The samples were taken in 40 enterprises 1974-1976. No local exhaust ventilation (spot ventilation) was used. The monthly geometric means of each method is given as percent of the grand geometric mean of the method, for metal are welding in stainless steel 3.8 mg/m³, for Tig in Al 1.1 mg/m³, for Mig in Al 10.4 mg/m³ and for the background in the work rooms 3.8 mg/m³1

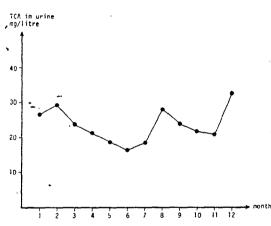


Fig. 4. The effect of the season. Geometric means of trichloracetic acid in urine taken in health controls on employees exposed to trichlorethylene in Sweden the years 1945, 1947, 1949, 1951, 1965, 1966, 1967, 1968 and 1969

tendency among employees to turn off the forced ventilation to avoid draught when outdoor temperatures are low in January through March. The variations between the days of the week is sometimes appreciable as observed e.g. in dry cleaning enterprises and metal industries where the exposure to trichloroethylene was at its peak in the middle of the week [3].

The situation with respect to work load in the industry may also influence the exposure. This situation follows a typical pattern over the year and should be considered for the particular branch under study. In the above example of exposure to dust in welding, the are time factor was observed. There was no significant difference in different months in the arc time factor indicating that the work intensity did not cause the variation.

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3.4 Errors in the Determination of Samples of Air Contaminants

The magnitude of the errors in the determinations of samples made one or two decades ago are rarely stated. This is so partly because a statistical view on analytical results is a rather recent accomplishment, even today not universally accepted by all analytical chemists.

Nowadays it is common to provide descriptions of analytical methods with data regarding precision [5]. Coefficients of variation in repeated analyses with a number of frequently used methods operated by the same operator are reported in the range 5–10% [5, 10]. This is an overestimation of the precision in the determination, however, when different laboratories and different methods and instruments are used.

In a series of interlaboratory calibrations, samples containing predetermined quantities of quartz, asbestos fibers or organic solvents where determined [18]. The limit of acceptance of a laboratory was for quartz and asbestos about $\pm\,30\%$ from the predetermined value and for organic solvents $\pm\,15\%$. The standard deviations and ranges in determinations of organic solvents are presented in the Table 3. This table shows that some laboratories make large errors, although fortunately this is rather rare.

The variation due to analysis is usually much less than the variation due to the sampling error at different times of e.g. the day. If a sample is taken e.g. in the inhaled air of an employee during one day and n determinations are made of the sample then the variance s^2 of the mean of the n determinations is composed of the variance s_1^2 in the true concentration of each sample and the variance s_2^2 in the determination of each sample: $s^2 = s_1^2 + s_2^2 / n$ [14]. In most cases only 1 determination is made of a sample and the equation is reduced to $s^2 = s_1^2 + s_2^2$. Usually the estimation of s_2^2 has to be based on repeated measurements of a few samples.

It can be safely assumed that most methods of determination have coefficients of variation far below e.g. 30%. To exemplify the importance of a coefficient of variation of 30% in the analytical determination it is assumed that the GSD of the true concentration values in one case is 1.60. Then the total GSD due to variation in the concentrations and in the determination will be about 1.70. The conclusion is that low precision in the determinations (e.g. about 30%) is usually not a serious drawback. The possibility of a considerable systematic error is a more important threat to the relevance of exposure data. The chances are good that large systematic errors have not been introduced in present day determinations since the methods have improved greatly during the past decade.

3.5 Random Errors

It is a well known fact that if the values of the independent variable in e.g. a regression analysis are encumbered by random errors, the regression coefficient found will be smaller than the regression coefficient determined from values of the independent variable without errors [14]. Random errors in measuring an exposure variable therefore tends to bias the slope of an exposure response line towards zero [9]. In practice this effect is usually unimportant in comparison with other biases discussed here, even in those rare cases where enough data are available to make a regression analysis of exposure vs response.

Table 3. Result of interlaboratory calibration [18]. Samples on charcoal tubes corresponding to 51 of air with a concentration in the range 5 times the permissible limit to one-fifth of the limit, s=the standard deviation, r=the range (lowest and highest values)

| Sub- Set 1 | Sub- | | | Set 2 | | | Set 4 | | | Set 5 | | |
|------------|------------------------------|-------------------------------|-------------------|------------------------------|------------|--------|------------------------------|------------|------------|------------------------------|-------------|------------|
| stance | Number of participating labs | _Z o;′ ₀ | r ⁰ /0 | Number of participating labs | <i>5</i> % | r% | Number of participating labs | <i>5</i> % | / % | Number of participating labs | <i>\$</i> % | <i>r</i> % |
| Styrene | 14 | 11 | 37-137 | 24 | 12 | 77-310 | 29 | 12 | 55-299 | _ | | _ |
| Tri | 9 | 11 | 82-181 | - | | _ | | _ | _ | 26 | 6 | 77-178 |
| Xylene | 13 | 11 | 31-134ª | 24 | 12 | 67-127 | 30 | 8 | 8-264 | 25 | 9 | 69-130 |

^{*} One laboratory reported concentrations about 10 times too high

U. Ulfvarsoi

4 Additional Factors Influencing Exposure to a Substrate

4.1 Part-time Exposure

It is rather unusual that an employee is occupied with a single operation during the whole workday or shift. As an example, in metal arc welding of nonalloy steel in workshops, the geometric mean of the arc time factor was 22% [31]. This applies for employees engaged full-time in welding, i.e. almost 80% of the time is used up for preparations before the welding or grinding, etc. after the welding.

Other causes of limited exposure which should be considered are the use of respirators and rotation of personnel, practised in e.g. the control of lead exposure in many countries [7]. If uptake is estimated from concentration data of air contaminants without considering limited exposure an appreciable positive bias will result.

4.2 Influence on Uptake of a Substance of Short-term Variations in Exposure

It is quite obvious that variations in concentrations of substances in the air within a day or shorter periods is important to the results. A single breath of air containing a very poisonous gas in a sufficiently high peak concentration may be fatal, although the average concentration of this gas over one day may be tolerable. This is an area of concern for accident prevention, however, and has very little to do with the monitoring of gases and vapours in order to check compliance with exposure limits.

In the simplest exposure model, response or effect is studied as a function of a single dose. This model of course is far from reality. A more complicated but still unrealistic model implies repeated doses of the same size. In reality the exposure will be composed of a complicated pattern of episodes with repeated doses of varying magnitude interrupted by breaks of varying lengths without exposure. Furthermore all exposed subjects in reality have an individual exposure pattern.

As has already been pointed out by Roach [23, 24], the durations of peak concentrations in relation to the biological half-life of the substance should be considered in judging exposure to air contaminants. The critical durations of peak concentrations and interruptions in the exposures are of the same magnitude as the biological half-life of the substance in the body. If the peak durations and the interruptions between peaks are much shorter than the biological half-life, the substance eventually will reach a concentration level in the body corresponding to the equilibrium at the average concentration in the air. If the durations of peaks are much longer than the biological half-life of the substance in the body, there will be enough time for the substance to accumulate to a concentration level in the body corresponding to the height of the peaks. The uptake will come into "resonance" with the environment, cf. Fig. 5, based on models suggested by others [13, 15, 22], further discussed in reference [27]. The implication of Fig. 5 is that although the average concentration is the same in the different exposure cases the uptake will be very different. It is possible that different organs in the body will respond differently to the exemplified exposure cases, e.g. one organ may respond to the area under the concentration-time curve, while a second organ may respond to the peak heights. Very little is known about this, but it is

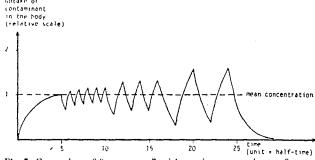


Fig. 5. Examples of "resonance" with environment, i.e. unfavourable exposure situations. Simple lirst order kinetic with main uptake and excretion via the lungs is assumed [22, 27]. In all exemplified exposure situations the average air concentration of the contaminant is the same (= 1 in the relative scale). The peaks of the body concentration will corresponded more and more closely to the peaks in the concentration in the air when the exposure episodes have a length at least as long as the biological half-life of the substance in the body observe that the diagrams should be read simultaneously and show what is assumed to happened at the same time in the inspiration air and the body!

suggested that when available data allow an investigation, the distribution of exposure over time should be considered. The possible bias is negative since the measured concentration is lower than the effective concentration during short periods.

5. Conclusions

Sampling strategies have been discussed almost exclusively with the view in mind of checking compliance with exposure limits or to some extent finding a basis for or checking control measures to decrease the exposure. Except for a few recent contributions [11, 12, 32] almost no efforts have been made to develop sampling strategies in order to describe the true uptake pattern of substances in the bodies of exposed employees and for obvious reasons: the ethical problem involved in prospective epidemiological studies [16] and the prohibitively high costs in making measurements when the future use of the measurements are uncertain.

Table 4. Bias in the estimation of uptake of a substance in a group of employees when uptake is deduced uncritically from various sources of information. += means that uptake is overrated, -= means that uptake is underrated in comparison with probable true uptake

| Premises of data | remises of data Cause of bias | | Validity of sign of bias | | |
|---|--|--------|--------------------------------|--|--|
| Measurements and uptake in | the same period and work place | | | | |
| Identification of the sub- stance | | | | | |
|) "Worst Case" | Biased sampling among employees | + | 3 | | |
| Monitoring daily averages | Biased sampling among employees | + or — | | | |
| General work area sampling | Biased sampling in the locality to find "hot spots" | + | 2 | | |
| Biologic sampling | Biased sampling among employees | + | 1 | | |
| Unconditioned, regular check-ups | No additional bias | 0 | 2 | | |
| No repeated measurement are made when the first result shows compliance | Biased sampling (the first result may have been unusually low) | _ | 2 | | |
| Measurements and uptake in the same period and "similar" work place | Biased sampling among enterprises | + | 2 | | |
| Measurements and uptake in | different periods of time | | | | |
| Measurements made in a period before uptake | Technical development | + | 2 | | |
| Measurements made in a period after uptake | Technical development | _ | 2 | | |
| Measurements and uptake in different seasons | Regular variations | + or | . _ | | |
| Other circumstances | | | | | |
| High exposure limit during measurements | Few data. Biased interpretation | _ | 1 | | |
| Rotation of employees to unexposed work | Invalidation of data | + | 3 | | |
| Use of effective respirator | Invalidation of data | + | 3 | | |
| Unfavourable exposure pattern | "Resonance" (cf. text) | _ | 2 | | |
| Hard physical labor | Increased lung ventilation | _ | 2 | | |

Code referring to the estimated validity of the suggested sign of bias: 3 = self evident; 2 = a conclusion with some reservation; 1 = an educated guess

Table 5. The consequence of the sign of bias in measurements on the error in standard setting

| Sign of bias | Interpretation | Effect on standard setting | Consequence |
|--------------|-------------------------|----------------------------|------------------|
| + | Observed conc. too high | Standart too high | "Health error" |
| _ | Observed conc. too low | Standard too low | "Economic error" |

To use the limited data available the investigator must have a reasonable idea of the sign of the bias in the estimated uptake. The bias may be due to a lack of representativeness or to additional circumstances, in the work situation. In Table 4 the probable bias of estimated uptake deduced from exposure data in an uncritical way is summarized. Some of the conclusions in Table 4 are self evident, others must be regarded more or less with reservations as discussed in some details in Section 2. The opinion of the author about the validity of the suggested signs of bias in Table 4 is expressed in the form of a code in the table. As has already been stated, if the exposure is overestimated the risk will be underestimated and vice versa. An inspection of the summaries of sings in the errors in Table 4 seems to suggest that overestimation of the uptake will be the most common outcome of judging the exposure from old data. The epidemiologist using old exposure data may use Table 4 as a checklist and try to find out the premises of his data and thus the most probable sign of bias. The implication of an overrated uptake is that exposure limits set will tend to be too high and the risk will be underrated ("health error"), cf. Table 5. It may be possible to some extent to counteract this simply by applying safer (= lower) exposure limits, but this may be possible only when the technical feasibility is obvious. In the long run there is no natural "safe side," since an exposure limit which is too low will cause unnecessary costs "economical error") affecting the possibilities of limiting more critical exposures. In the future, filed exposure data should be accompanied by all information necessary to judge their validity. The following factors should be considered.

- (a) The name and nature of the operation(s) going on, products used and manufactured (declaration of content), contaminants formed.
- (b) The average proportion of time used for the operation per day, week, year.
- (c) Regular use of respirators, rotation of employees, notation of hard physical labour of the employees.
- (d) Why, when, where and how the sampling was performed.
- (e) Analytical method.
- (f) Exposure limit at the time of sampling.

References

- Ahlmark A, Gerhardsson L (1981) The silicosis in Sweden since 1930 (in Swedish). Arbete och Hälsa 1981: 15. Arbetarskyddsverket, Stockholm. 55 sid, 1 bilaga
- 2. Aitchison J, Brown JAC (1976) The lognormal distribution with special reference to its uses in economics. Cambridge University Press, Cambridge, p 176

- Andersson A (1957) Gesundheitliche Gefahren in der Industrie bei Exposition für Trichloräthylen. Acta Med Scand [Suppl] 323:220
- 4. Andersson I-M, Rosén G (1979) Solvent exposure in paint manufactoring. An investigation of 51 employees at 8 paint factories. Undersökningsrapport 18: Arbetarskyddsstyrelsen, arbetsmedicinska avdelningen, Stockholm (29 sidor) (in Swedish)
- Anonymous (1977) NIOSH manual of analytical methods, vol 1, 2nd Ed. DHEW (NIOSH)
 Publication No. 77-157-A. U.S. Dept of Health, Education and Welfare, Public Health
 Service, Cincinnati, Ohio
- Anonymous (1982) Threshold limit values for chemical substances in workroom air adopted by American Conference of Governmental Industrial Hygienists. ACGIH 6500 Glenway Ave, Bldg D-5 Cincinnati, OH 45211
- 7. Anonymous (1979) Criteria documentation on inorganic lead. Arbete och Hälsa 1:24: Arbetarskyddsverket, Stockholm, p 55 (in Swedish)
- Anonymous (1981) Permissible exposure limits (in Swedish). AFS 1981: 8. Arbetarskyddsverket, Stockholm, 39 sid
- 9. Armstrong BG (1982) Effects of approximation in exposure assessments on estimates of exposure response relationships. Scand J Work Environ Health [Suppl] 8:20-23
- Corn M, Esmen NA (1979) Workplace exposure zones for classification of employee exposures to physical and chemical agents. Am Ind Hyg Assoc J 40:47-57
- 11. Esmen N (1979) Retrospective industrial hygiene surveys. Am Ind Hyg Assoc J 40:58-65
- 12. Gamble J, Spirtas R (1976) Job classification and utilization of complete work histories in occupational epidemiology. J Occup Med 18:399-404
- Haggard HW (1924) The absorption, distribution and elimination of ethyl ether. J Biol Chem 59:753-770
- Hald A (1960) Statistical theory with engineering applications,. John Wiley & Sons, Inc, New York London, p 783
- 15. Henderson Y, Haggard HW (1924) Noxius gases. Reihold Publ Comp, New York
- Hernberg S (1974) Epidemiologic methods in occupational health research. Work, Environ, Health 11:59-68
- Hernberg S, Tola S, Vaaranen V (1978) The occupational exposure to lead has decreased in Finland. 27th meeting on occupational hygiene in Denmark. 20-22 November 1978. Arbejdsmiljöinstituttet, Arbejdstilsynet, Danmark (in Swedish)
- Krantz S, Lindstedt S, Lundgren L, Palmqvist U, Tillman C, Ulfvarson U (1983) Interlaboratory control of airanalyses in occupational hygiene. To be published in Arbete och Hälsa. Arbetarskyddsverket, Stockholm (in Swedish)
- Leidel NA, Busch KA, Lynch JR (1977) Occupational exposure sampling stategy manual.
 U.S. Department of Health, Education and Welfare. DHEW (NIOSH) Publ No. 77-173
- Leidel NA, Busch KA, Crouse WE (1975) Exposure measurement action level and occupational environment variability. HEW Publication No. 76-131 (NIOSH). Dept of Health, Education and Welfare, Public Health Service, NIOSH, Cincinnati, Ohio, p 38
- 21. MacMahon B, Pugh TF (1970) Epidemiology. Little & Co., Boston
- Riggs DS (1963) The mathematical approach to physiological problems. Williams & Wilins Co, Baltimore
- 23. Roach SA (1966) A more rational basis for air sampling programs. Am Ind Hyg Ass J 27: 1-
- 24. Roach SA (1977) A most rational basis for air sampling programmes. Am Occup Hyg 20:
- 25. Sherwood RJ, Greenhalgh DMS (1960) A personal air sampler. Ann Occup Hyg 2: 127-132
- Ulivarson U, Rosén G, Cardfelt M, Ekholm U (1975) Chemical hazards in the paint industry. dnr 4979/75 (64-sidor). Färgindustrins Arbetsmiljö, Branschutredning med stöd från arbetarskyddsfonden. Del I. Kemiska hälsorisker (in Swedish)
- 27. Ulfvarson U, Övrum P (1976) Distribution of organic solvents between blood and air. Arbete och Hälsa 1976: 7. Arbetskyddsverket, Stockholm, p 20 (in Swedish)
- 28. Ulfvarson U (1977) Statistical evaluation of the results of measurements of occupational exposure to air contaminants. Scand J Work Environ Health 3:109-115

- 29. Ulfvarson U (1977) Chemical hazards in the paint industry. International symposium on the control of air pollution in the working environment. Stockholm 6-8 Sept. 1977. Part II. solvents - welding, pp 62-75. International Labour Office, Geneva and Worker's Protection Fund, Stockholm
- Ulfvarson U, Hallne U, Bellander T (1978) Welding problems connected with work environment.
 Welding in stainless steel with metal arc-welding with covered electrodes and gas-shielded welding.
 Survey of air contaminants (in Swedish). Arbetarskyddsverket, Stockholm 1978, 1-52b Arbete och Hälsa 1978:6
- 31. Ulfvarson U (1981) Survey of air contaminants from welding. Scand J Work Environ Health [Suppl] 7:2-28
- 32. Vihma T (1981) Health hazards and stress factors in small industry prevalence study in the province of Uusimaa with special reference to the type of industry and the occupational title as classifications for the description of occupational health problems. Scand J Work Environ Health [Suppl] 7:3-149

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BENEFIT-COST ANALYSIS OF ENVIRONMENTAL REGULATION: CASE STUDIES OF HAZARDOUS AIR POLLUTANTS

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Regulating toxic chemicals is highly controversial, yet it promises to be a major task confronting an industrial society. Increasing attention to toxic substances reflects in part recent growth in the number and quantity of man-made chemicals. As controls over the conventional pollutants take effect, toxic substances move to center stage in the political arena. This increased attention also stems from the fact that many of the statutes and regulatory procedures developed for the conventional pollutants are ill-suited to the new substances.

The Administrator of the Environmental Protection Agency, William Ruckelshaus, has urged Congress to reconsider the present statutory framework for regulating toxic air pollutants. EPA may shift its regulatory strategy from the identification of specific control technology and

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^{1.} See Statement by W. Ruckelshaus, Administrator of the EPA, Before the Sub-comm. on Oversight & Investigations of the House Comm. on Energy & Commerce 10-11 (Nov. 7, 1983) (listing the specific problems experienced in implementing section 112) [hereinafter cited as Statement by Ruckelshaus].

evaluation of the industry's ability to afford controls² to a strategy that weighs the trade-offs between control costs and risk reduction.³

This article evaluates alternative methods of integrating benefit-cost considerations into the regulation of toxic substances. The use of benefitcost considerations in this context is highly controversial and widely debated. The debate, however, has incorporated little or no reference to specific decisions made by environmental policy makers. Proponents of benefit-cost analysis point to the general virtues of explicit evaluation of benefits and costs. Critics, on the other hand, stress the philosophical difficulties involved in making judgments about life and death⁵ or the practical difficulty of estimating the costs and benefits of control.6 These broad debates do not consider what is at stake in particular circumstances and, indeed, whether those who assess the scientific evidence very differently might find much common ground in actual regulatory decisions. This article attempts to fill that gap by considering three toxic pollutants - benzene, coke oven emissions, and acrylonitrile. All three pollutants are currently considered targets for control under section 112 of the Clean Air Act.7

This article focuses on the ideas that benefit-cost principles can help to identify regulatory alternatives and that benefit-cost analysis can yield widely accepted policy recommendations despite large uncertainties in many parameter estimates. Critics caricature benefit-cost analysis as a mindless toting up of costs and benefits, but benefit-cost principles are

-2. Id. at 20.

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more properly viewed as a framework for exploring opportunities to increase health and other benefits or reduce unnecessary costs. The crucial concept is marginalism. Given an existing regulation, benefit-cost analysis identifies marginal changes that increase benefits more than costs, or decrease costs more than benefits.8

Critics argue that the data on benefits and costs of regulatory alternatives are simply too uncertain to use risk assessment or benefit-cost results in policymaking. In some cases, however, all plausible estimates of the parameters lead to the same policy recommendation. Thus, the results in such cases remain robust with respect to uncertainty. Two of the three case studies evaluated in this paper fall in this category. Uncertainty, therefore, should not serve to dismiss out-of-hand benefit-cost analysis in environmental regulation.

The first Part of this article discusses section 112 of the Clean Air Act, which provides the framework for regulating the three case-study pollutants. Part II presents the three case studies and includes an analysis of regulatory alternatives for the three pollutants. The next Part summarizes the uncertainties in calculating regulatory benefits, and the effect of those uncertainties on policy recommendations. Finally, Part IV outlines the overall conclusions derived from examining the case studies.

I. REGULATORY CONTROLS

A. Section 112 of the Clean Air Act

Section 112 provides the statutory authority for regulating "hazardous" air pollutants emitted from stationary sources. 15 That section reflects he need to regulate hazardous pollutants outside the complex framework

^{3.} See W. Ruckelshaus, Administrator of the EPA, Science, Risk and Policy 10 (June 22, 1973) (speech to the National Academy of Sciences). See also W. Ruckelshaus, Administrator of the EPA, Risk in a Free Society (Feb. 18, 1984) (speech at Princeton University); speech by J. Cannon, EPA Asst. Administrator for Air and Radiation, to the Natural Resources Law Section of the American Bar Association (Mar. 10, 1984).

^{4.} See, e.g., Crandall, The Use of Cost-Benefit Analysis in Regulatory Decisions, in MANAGEMENT OF ASSESSED RISK FOR CARCINOGENS 99-107 (W. Nicholson ed. 1981) (defending the general applicability of benefit-cost analysis to regulatory decisionmaking); Harrison, Cost-Benefit Analysis and the Regulation of Environmental Carcinogens, in MANAGEMENT OF ASSESSED RISK FOR CARCINOGENS 109-22 (W. Nicholson ed. 1981) (evaluating the advantages of using benefit-cost principles in regulating carcinogens); Ashford, Alternatives to Cost-Benefit Analysis in Regulatory Decisions, in MANAGEMENT OF ASSESSED RISK FOR CARCINOGENS 129-37 (W. Nicholson ed. 1981) (discussing the general limitations of benefit-cost analysis in regulatory decisionmaking).

^{5.} See, e.g., S. Kelman, What Price Incentives? 27-88 (1981) (summarizing the ethical concerns involved in using the market for pollution control); Kelman, Cost-Benefit Analysis and Environmental, Safety, and Health Regulation: Ethical and Philosophical Considerations, in Cost-Benefit Analysis and Environmental Regulations: Pollics, Ethics, and Methods 137-54 (D. Swartzman, R. Likoff & K. Croke eds. 1982).

^{6.} See, e.g., Ashford, supra note 4, at 129-37.

^{7, 42} U.S.C. § 7412 (Supp. V 1981). Although this article provides background information on the provisions and history of section 112 to place the specific case studies discussed in context, its analysis is not restricted to regulatory alternatives permitted by the current statute. Thus, some of the alternatives that it considers might require statutory changes.

^{8.} The technology-based standards that the EPA has promulgated provide a basis for valuating the benefits and costs of those standards and for a detailed investigation of tgulatory alternatives.

^{9.} See, e.g., Hurter, Tolley & Fabian, Benefit-Cost Analysis and the Common Sense Environmental Policy, in Cost-Benefit Analysis and Environmental Regulaions: Politics, Ethics, and Methods 92-99 (D. Swartzman, R. Likoff & K. Croke eds., 82) (discussing the potential sources of uncertainty in comparing the benefits and costs environmental programs).

^{10.} See infra text accompanying note 109. See also infra Table 1.

^{11.} See infra notes 15-56 and accompanying text.

^{12.} See infra notes 57-140 and accompanying text. A more detailed analysis of these se studies has been presented in an earlier manuscript. Haigh, Harrison & Nichols, nefits Assessment and Environmental Regulation: Case Studies of Hazardous Air Pollants (July 1983) (unpublished manuscript available upon request from the authors).

^{13.} See infra notes 141-220 and accompanying text.

^{14.} See infra notes 221-228 and accompanying text.

^{15. 42} U.S.C. § 7412 (Supp. V 1981).

of ambient standards, state implementation plans, and new source performance standards established for the more ubiquitous "criteria" pollutants. The Act defines a hazardous air pollutant as one "to which no ambient air quality standard is applicable and which in the judgment of the Administrator causes, or contributes to, air pollution which may reasonably be anticipated to result in mortality or an increase in serious irreversible, or incapacitating reversible, illness." Section 112 requires the EPA Administrator to establish a list of hazardous air pollutants and, within 180 days of listing a substance, to set emission standards for sources "at the level which . . . provides an ample margin of safety to protect the public health."

The language of section 112 emerged as a compromise from the House-Senate conference committee on the Clean Air Act amendments of 1970. The House bill proposed basing national emission standards for hazardous air pollutants on technological and economic feasibility. In contrast, Senator Edmund Muskie and his supporters in the Senate

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[I]t is urgent that Congress adopt new clean air legislation which will make possible the more expeditious imposition of specific emission standards both for mobile and stationary sources and the effective enforcement of such standards by both State and Federal agencies . . . Therefore, particular attention must be given to new stationary sources which are known to be either particulary large-scale polluters or where the pollutants are extrahazardous.

H.R. REP. No. 1146, 91st Cong., 2d Sess. 5, reprinted in 1970 U.S. Code Cong. & Ad. News 5356, 5360-61.

- 17. 42 U.S.C. § 7412 (Supp. V 1981).
- 18. Section 112(b) provides that:

(1)(A) The administrator shall, within 90 days after December 31, 1970, publish (and shall from time to time thereafter revise) a list which includes each hazardous air pollutant for which he intends to establish an emission standard under this section.

- (B) Within 180 days after the inclusion of any air pollutant in such list, the Administrator shall publish proposed regulations establishing emission standards for such pollutant together with a notice of a public hearing within thirty days. Not later than 180 days after such publication, the Administrator shall prescribe an emission standard for such pollutant, unless he finds, on the basis of information presented at such hearings, that such pollutant clearly is not a hazardous air pollutant. The Administrator shall establish any such standard at the level which in his judgment provides an ample margin of safety to protect the public health from such hazardous air pollutant.
- Id. § 7412(b).
- 19. H.R. REP. No. 1783, 91st Cong., 2d Sess. 10-12, 45-47, reprinted in 1970 U.S. CODE CONG. & AD. NEWS 5356, 5378-79.
 - 20. The relevant section provided that:
 - (a) For the purpose of preventing the occurrence of significant new air pollution problems arising from or associated with any class of new stationary sources which, because of the nature or amount of emissions therefrom, may contribute substantially to endangerment of the public health or welfare, the Secretary shall from time to time by regulation, giving appropriate consideration to technological and economic feasibility, establish standards with respect to such emissions
 - (b) Such emission standards shall provide that -
 - (1) If such emissions are extremely hazardous to health, no new source of such emissions shall be constructed or operated, except where (and subject to such conditions as he deems

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favored a zero-discharge requirement, which would have applied to fewer pollutants than the House bill.²¹ The final language of the section, however, refers neither to technological feasibility nor to zero discharges.²² This suggests that, while the conference committee expected health considerations to determine standards, it did not expect health protection to require the absolute elimination of all hazardous emissions.

B. Dilemmas in Implementation

EPA's regulatory activity under section 112 over the past thirteen years has been modest.²³ Emission standards have been promulgated for

necessary and appropriate) the Secretary makes a specific exemption with respect to such construction or operation.

(2) In the case of other emissions, any new source of such emissions shall be designed and equipped to prevent and control such emissions to the fullest extent compatible with the available technology and economic feasibility, as determined by the Secretary.

H.R. REP. No. 1146, 91st Cong., 2d Sess. 35 (1970).

21. Bonine, The Evolution of 'Technology-Forcing' in the Clean Air Act, [Monograph No. 21] 6 ENV'T REP. (BNA) 7 (July 25, 1975). The Senate report indicated its determination "that existing sources of pollutants should meet the standard of the law or be closed down, and in addition, that new sources should be controlled to the maximum extent possible to prevent atmospheric emissions." S. REP. No. 1196, 91st Cong., 2d Sess. 2-3 (1970). Later, however, the report says that "[i]n writing a relatively restrictive definition of hazardous agents, the Committee recognized that a total prohibition on emissions is a step that ought to be taken only where a danger to health, as defined, exists." Id. at 20.

The bill provided in part that:

- (a) (1) The Secretary shall, within ninety days after the enactment of this section and from time to time thereafter, publish in the Federal Register a list of those air pollution agents or combination of such agents which available material evidence indicates are hazardous to the health of persons and which shall be subject to a prohibition or emission standard established under this section.
- (2) Within one hundred and eighty days after the publication of such list, or revision thereof, the Secretary, in accordance with section 553 of title 5 of the United States Code, shall publish a proposed prohibition and a notice of a public hearing within thirty days. As soon as possible after such hearing, but not later than six months after such publication, the Secretary shall promulgate such prohibition, unless, based upon a preponderance of evidence adduced at such hearing, he finds within such period and publishes his finding—
 - (A) that such agent is not hazardous to the health of persons; or
- (B) that a departure from such prohibition for stationary sources will not be hazardous to the health of persons.
- (3) If the Secretary finds under paragraph (2)(A) of this subsection that such agent is not hazardous to the health of persons, he shall immediately publish an emissions standard in accordance with the procedures established under section 114 of this Act.
- (4) If the Secretary finds under paragraph (2)(B) of this subsection that a departure from such prohibition for any stationary source will not be hazardous to the health of persons, he shall immediately promulgate an emission standard for such agent or combination of agents from any such stationary source to protect the health of persons.

Id. at 95-96.

22. See supra note 18.

23. See generally Doniger, Federal Regulation of Vinyl Chloride: A Short Course in Law and Policy of Toxic Substances Control, 7 Ecology L.Q. 497, 565-85 (1978); Currie, Direct Federal Regulation of Stationary Sources Under the Clean Air Act, 128 U. PA. L. Rev. 1389 (1980) (generally discussing regulatory activity under section 112).

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only four substances: beryllium, asbestos, mercury, and vinyl chloride.²⁴ The EPA has listed three additional substances: benzene, radionuclides, and inorganic arsenic.²⁵

Both EPA and the environmental groups monitoring the agency's actions under section 112 have concentrated on pollutants suspected of causing cancer.²⁶ The focus on carcinogens creates a dilemma for the agency because many scientists believe that there are no thresholds for carcinogens — no exposure levels short of zero that are risk free.²⁷ Thus, a strict interpretation of section 112's requirement to provide "an ample margin of safety" would require zero-discharge standards, tantamount to banning the listed substances.

Such a strict interpretation of section 112 could be impractical. Many substances subject to regulation under section 112 are important industrial chemicals. Zero-discharge limitations on these substances would lead to numerous plant closures and the loss to consumers of many valuable products. Consequently, EPA has avoided a strict interpretation of section 112 and instead has proposed standards requiring the degree of control achievable with the "best available technology" (BAT). Standards promulgated by the EPA for asbestos and vinyl chloride illustrate the agency's dilemma and its eventual decision to base control requirements on technological feasibility.

In 1971, EPA proposed standards for asbestos because of its link to a form of cancer known as asbestosis. ³⁰ Public comments on the proposed standards revealed no scientific doubt about asbestos hazards, but also stressed the importance of asbestos to the economy. ³¹ Although the EPA maintained that the final standard "was not based on economic considerations" ³² and that "the overriding considerations are health effects, "³³ the preamble to the standard acknowledged the dilemma:

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EPA considered the possibility of banning production, processing, and use of asbestos or banning all emissions . . . into the atmosphere, but rejected these approaches Either approach would result in the prohibition of many activities which are extremely important; moreover, the available evidence relating to the health hazards of asbestos does not suggest that such prohibition is necessary to protect public health. ¹⁴

The effect of this dilemma on EPA action is indicated by the fact that the agency did not even adopt this compromise standard until 1973 (well beyond the 180-day limit), and then only after a court order.³⁵

The language of the vinyl chloride standard, promulgated in October 1976, 36 provides an even clearer indication of the adoption of a technology-based approach. In the proposed regulation, EPA interpreted section 112 as allowing it to set standards:

that require emission reduction to the lowest level achievable by use of the best available control technology in cases involving apparent non-threshold pollutants, where complete emission prohibitions would result in wide-spread industry closure and EPA has determined that the cost of such closure would be grossly disproportionate to the benefits of removing the risk that would remain after imposition of the best available control technology.³⁷

Thus, although section 112 mentions only health effects, and a literal reading might require that all emissions of non-threshold pollutants be banned, the EPA developed an accommodation that bases control on technological feasibility.

EPA did not identify guidelines for listing substances under section 112 in its standards for asbestos or vinyl chloride. Asbestos and vinyl chloride presented clear cases of proven carcinogens, but over fifty other substances are identified only as potentially hazardous air pollutants.³⁸ In contrast, many toxic water pollutants were listed (and a schedule for developing regulations established) in 1976 as part of a consent decree with the Natural Resources Defense Council.³⁹

Environmental groups became dissatisfied with the slow pace at which the agency was listing substances and promulgating standards under section 112.40 In November 1977, the Environmental Defense Fund

^{24. 40} C.F.R. §§ 61.20-.34, 61.50-.55 (1979) (promulgating emission standards for asbestos, beryllium and mercury); 40 C.F.R. §§ 61.60-.71 (1979) (promulgating emission standards for vinyl chloride).

^{25. 42} Fed. Reg. 29,332 (1977) (listing benzene as a hazardous air pollutant); 44 Fed. Reg. 76,738 (1979) (listing radionuclides as a hazardous air pollutant); 48 Fed. Reg. 33,112 (1983) (listing inorganic arsenic as a hazardous air pollutant).

^{26.} See Statement by W. Ruckelshaus, Administrator of the EPA, Before the Subcomm. on Health & the Env't of the House Comm. on Energy & Commerce 10 (Mar. 29, 1984) [hereinafter cited as 1984 Statement by Ruckelshaus].

^{27.} See Industrial Union Dept. v. American Petroleum Inst., 448 U.S. 607, 624 (1980).

^{28. 1984} Statement by Ruckelshaus, supra note 26, at 13.

^{29.} As discussed in more detail below, a "generic" policy proposed in 1979 would have formalized the agency's implicit policy of requiring, at a minimum, BAT controls for sources emitting pollutants listed under section 112. See infra text accompanying notes 43-50

^{30. 40} C.F.R. §§ 61.20-.25 (1971).

^{31. 38} Fed. Reg. 8820, 8822 (1973).

^{32.} Id.

^{33. 40} C.F.R. §§ 61.20-.25 (1971).

^{34. 38} Fed. Reg. 8820, 8822 (1973).

^{35.} Id.

^{36. 40} C.F.R. §§ 61.60-.71 (1976).

^{37. 40} Fed. Reg. 59,534 (1975).

^{38. 44} Fed. Reg. 58,642, 58,643 (1979).

^{39.} Natural Resources Defense Council v. Train, 8 Env't Rep. Cas. (BNA) 2120 (D.D.C. 1976).

^{40.} See, e.g., Doniger, supra note 23, at 565-85 (discussing the politics underlying EPA's promulgation of a vinyl chloride standard).

(EDF) filed a petition requesting that EPA establish the terms of the vinyl chloride agreement as a generic approach to the regulation of all carcinogens. Finally, in October 1979, EPA proposed a cancer policy entitled Policies and Procedures for Identifying, Assessing, and Regulating Airborne Substances Posing a Risk of Cancer. Although the proposed policy was never promulgated, a review of its provisions provides an indication of the procedures that evolved over the first decade of section 112's existence.

C. Cancer Policy

The most important features of the EPA's proposed "cancer policy" involved the criteria for listing substances and the criteria for setting standards for source categories. The proposal established a relatively low hurdle for listing; EPA would list any substance having a high probability of carcinogenicity unless there was no evidence of a significant threat of ambient exposure from emissions by stationary sources. Upon listing, a set of generic regulations including maintenance, storage, and "housekeeping" requirements would immediately apply to sources emitting the substance. 45

For each listed substance, the EPA would prepare detailed estimates of health effects and use those estimates to set priorities to develop emission standards for individual source categories posing the most imminent threat to the public health. The emission standards would, at a minimum, require BAT controls. The procedures for determining BAT do not involve risk assessment. Quantitative risk estimates would, however, be employed in the standard-setting process if they showed that the residual risk after BAT controls was "unreasonable." In such a case, EPA would impose tighter controls. The procedures detailed estimates and the residual risk after BAT controls was "unreasonable." In such a case, EPA would impose tighter controls.

41. See Doniger, supra note 23, at 584.

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In sum, EPA's record in implementing section 112 has consisted of much study and little regulation. The proposed cancer policy did create a methodology that would have allowed vastly greater listings, but would also have severely limited EPA discretion in setting specific standards for listed substances. In the last several years, the EPA has continued to analyze potential section 112 pollutants, but has not listed any new substances, nor proposed new standards for substances previously listed, nor promulgated standards proposed earlier. The following statement made by David Patrick, the chief of the Pollutant Assessment Branch in the Office of Air Quality Planning and Standards at EPA, illustrates the concerns of the agency:

All have perceived that a literal interpretation of section 112 would not preclude open-ended control requirements or the possibility of zero emission goals, regardless of the control costs. Given this potential and the apparent lack of flexibility regarding the removal of substances from the list of hazardous pollutants or the exclusion of source categories from control requirements, the Agency has also been reluctant to list pollutants as hazardous without some reasonable assurance that subsequent regulations would convey health benefits that are not grossly disproportionate to the costs of control.⁵⁰

D. Recent Congressional Debate

In the current debate on reauthorization of the Clean Air Act, environmental groups have criticized EPA's review process as "slow and repetitive." The Environmental Defense Fund has urged Congress to: (1) adopt a generic method for listing airborne carcinogens; (2) list the thirty-seven substances now under study; and (3) require that EPA develop a systematic regulatory approach that includes literature reviews, periodic reports, and time limits for action. In contrast, the Chemical Manufacturers Association (CMA) advocates modifying section 112 to allow EPA to regulate only those substances that pose a significant risk to health and to consider social, technical, energy, and economic consequences in setting standards. Finally, EPA Administrator Ruckelshaus advocates a regulatory strategy that is based on the balancing of

^{42. 44} Fed. Reg. 58,642 (1979). The proposal was part of a larger effort by the Carter administration to develop regulatory policies for carcinogens. A controversial cancer policy proposed by the Occupational Safety and Health Administration (OSHA) preceded the EPA document, see 45 Fed. Reg. 5002 (1980). In addition, the heads of the four major regulatory agencies dealing with carcinogens had formed the Interagency Regulatory Liaison Group. That group had a mandate to develop a greater scientific consensus on cancer risk assessment procedures. Id. at 58,647. Finally, in 1979 EPA was developing regulations on benzene emissions under section 112 to be used as a prototype for the procedure the agency was elaborating in its generic policy. Indeed, when the White House Regulatory Analysis Review Group selected the EPA cancer policy for review, the agency suggested that the group use benzene as an indicator of how the policy would be implemented. See Nichols, The Regulation of Airborne Benzene, in Incentives for Environmental Protection 148 (T. Schelling ed. 1983).

^{43.} See 44 Fed. Reg. 58,642 (1979).

^{44.} Id. at 58,654.

^{45.} Id. at 58,648. See also 44 Fed. Reg. 58,662-70 (1979).

^{46. 44} Fed. Reg. 58,642, 58,654 (1979).

^{47.} Id.

^{48.} See supra text accompanying notes 45-47. See also Harrison, supra note 4, at 112-13.

^{49.} See [14 Curr. Dev.] ENV'T REP. (BNA) 1109-11. But see infra notes 216-220 and accompanying text (discussing the recent developments in regulation under Section 112).

^{50.} See D. Patrick, Air Toxics: Regulation and Research 3 (Apr. 6, 1982) (speech presented at the Air Pollution Control Association (APCA) Conference, Houston, Tex.). See also Harrison, supra note 44, at 112-13 (critiquing EPA's proposed cancer policy).

^{51.} D. Doniger, Statement on Behalf of the National Clean Air Coalition, Before the Subcomm. on Oversight & Investigations of the House Comm. on Energy & Commerce 10 (Nov. 7, 1983).

^{52.} Doniger, supra note 23, at 579-84.

^{53. [11} Curr. Dev.] ENV'T REP. (BNA) 1026 (1981).

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many factors including the nature of the risk posed by a substance and the cost of eliminating or minimizing it.⁵⁴

The eventual result of this debate over section 112 cannot yet be determined. Thus far, however, sentiment in the House seems to favor swifter, more aggressive regulation of airborne carcinogens. In August 1982, the House Energy and Commerce Committee voted in favor of an amendment requiring that, in each of the next four years, EPA review twenty-five percent of the thirty-seven substances discussed earlier. The amendment would create a presumption in favor of listing; each of the thirty-seven substances would be listed automatically unless EPA determined that it was not hazardous. If this provision, or a similar one, is enacted, the pace of regulation under section 112 should reach substantially higher levels than ever before.

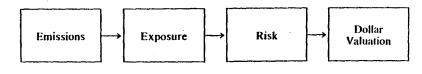
II. THE CASE STUDIES

A. Steps in Estimating Benefits

These studies estimate the benefits of pollution control standards by tracing the links from emissions to exposure to risk. The purposes of the analysis are either to estimate the dollar value that affected parties place on the reduced risk or to use the risk estimates to calculate the implicit cost per statistical life saved. The steps used, presented schematically in Figure 1, apply in assessing the benefits of controlling virtually any dangerous pollutant. The following discussion provides a general overview of the calculations associated with each step in the context of regulating airborne carcinogens.

The change in emissions due to regulation is the most straightforward of the calculations that produce benefit estimates. For each plant, the

Figure 1: Steps in Estimating Benefits



^{54. 1984} Statement by Ruckelshaus supra note 26, at 14.

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EPA estimates the emissions with and without controls in place.⁵⁸ The difference between these two estimates equals the emissions reduction attributable to the regulation imposed.

Emissions reduction estimates are converted into more meaningful estimates of exposure reductions by calculating an "exposure factor" for individual plants. ⁵⁹ The exposure factor indicates the amount of exposure caused by a unit of emissions from a particular source. ⁶⁰ Both the dispersion pattern of emissions and the population pattern in the area surrounding the plant contribute to calculating this factor.

In many cases, EPA estimates emissions dispersion using a "model plant." For a given level of emissions, the dispersion model uses meteorological data to generate estimates of average annual pollutant concentrations at various distances from the source. The estimated concentrations are then combined with plant-specific population data to estimate total exposure levels for a given level of emissions.

Exposure levels are expressed in terms of "µg/m³-person-years," which is simply the average annual concentration (in micrograms per cubic meter) multiplied by the number of people exposed and the period of exposure.⁶² This summary measure of exposure provides sufficient information to predict total risk under certain conditions.⁶³ Dividing the exposure level by the total level of emissions gives the exposure factor, expressed in terms of µg/m³-person-years per kilogram emitted.

Reduced exposure is translated into reduced risk using the unit risk factor for the particular pollutant. A unit risk factor represents the risk of cancer posed by exposure to one unit of a substance — measured as the risk of cancer per µg/m³-person-year.64

Each of the three case studies used unit risk estimates prepared by EPA's Carcinogen Assessment Group (CAG). The CAG unit risk estimate measures the increased probability of cancer resulting from exposure to 1 µg/m³ for a lifetime.⁶⁵ This figure divided by seventy equals the risk of

^{55. [13} Curr. Dev.] Env't Rep. (BNA) 491 (1982).

^{36.} Id.

^{57.} But see infra notes 141-51 and accompanying text (discussing the uncertainties inherent in this analysis).

^{58.} See Office of Air Quality Planning & Standards, U.S. Envtl. Protection Agency, Benzene Emissions from Maleic Anhydride Industry — Background Information for Proposed Standards, Table 1-5 (Feb. 1980 draft) [hereinafter cited as Benzene Emissions Background Information].

^{59.} If a plant with an exposure factor of 0.6 μ g/m³-person-years/kg reduces its emissions by 1 million kilograms, for example, exposure falls by 0.6(1,000,000) = 600,000 μ g/m³-person-years.

^{60.} See Nichols, supra note 42, at 187-88.

^{61.} See, e.g., Benzene Emissions Background Information, supra note 58, at E.8.

^{62.} Thus, for example, 1000 people exposed, on average, to 10 μg/m³ for one year generate 10,000 μg/m³-person-years of exposure, as do 10,000 people exposed to 1 μg/m³.

^{63.} Such risk is independent of how total exposure is distributed across the population if risk is proportional to exposure. See infra notes 164-171 and accompanying text.

^{64.} The risk of getting cancer obviously varies with the carcinogenicity of the substance. See infra notes 164-183 and accompanying text (discussing the difficulties of extrapolating from low to high doses).

^{65.} CAG considers a lifetime to be seventy years; hence, in this study the CAG's estimated exposure factor is divided by seventy to obtain an annual estimate. See, c.g., Carcinogen Assessment Group, Office of Health & Envtl. Assessment, U.S. Envtl. Pro-

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cancer per μg/m³-person-year. In applying epidemiological data, the CAG employs a procedure that assumes that risk remains proportional to dose at low levels of exposure.66

Over the past decade or two, a substantial literature has accumulated on the issue of valuing reductions in risks to life.⁶⁷ Economists agree that the appropriate criterion is "willingness to pay.¹⁶⁸ The principle is a simple one: an individual values each benefit just as much as the amount he would be willing to pay to secure it.

Inferences drawn from actual behavior provide the best estimates of willingness to pay. Many studies have estimated willingness to pay for reduced risks to life based on the wage premiums associated with occupational risks. Bailey has reviewed several empirical studies, adjusting them for consistency. His estimate covers a range of \$170,000 to \$715,000 per life saved, with an intermediate estimate of \$360,000 in 1978 dollars, or approximately \$500,000 in 1982 dollars. Other studies, however, have estimated much higher wage premiums for occupational risks, with the highest estimates in excess of \$5 million per life saved in 1982 dollars. Thus, the published estimates from wage studies range from several hundred thousand dollars to several million dollars per statistical life saved.

Many of the calculations in this article forgo the final step of placing a dollar value on lives saved and presenting a single net benefit result. However, estimates of the reductions in lives saved and the implicit cost per statistical life saved are presented. These results are then compared

tection Agency, Carcinogen Assessment Group's Final Report on Population Risk to Ambient Benzene Exposures 12 (1977) [hereinafter cited as Final EPA Benzene Assessment].

66. Id. at 2.

67. See, e.g., Zeckhauser, Procedures for Valuing Life, 23 PUB. POL'Y 419 (1975); Graham & Vaupel, Value of a Life: What Difference Does it Make?, I RISK ANALYSIS 89

68. See Schelling, The Life You Save May Be Your Own, in PROBLEMS IN PUBLIC EXPENDITURE ANALYSIS 127, 142-58 (S. Chase ed. 1968). Schelling is generally credited with being the first to argue that willingness to pay for risk reduction is the appropriate conceptual approach to valuing "life saving." A slightly different formulation, which should yield virtually identical results when dealing with small risks, is to ask how much money an individual would have to receive to forgo the benefit.

The technical terms for these two measures are "compensating variation" (CV) and "equivalent variation" (EV). In general, when discussing risk reductions, EV (how much money an individual would have to receive to be willing to go without the risk reduction) will exceed CV because of income effects. For small changes in risk, however, the differences between the two measures will be negligible.

69. See Thaler & Rosen, The Value of Saving a Life: Evidence from the Labor Market, in HOUSEHOLD PRODUCTION AND CONSUMPTION 265-301 (N. Terleckyj ed. 1976); G. Blomquist, Valuation of Life: Implications of Automobile Seat Belt Use (1977) (Ph.D. dissertation, University of Chicago); A. Dillingham, The Injury Risk Structure of Occupations and Wages (1979) (Ph.D. dissertation, Cornell University).

70. See M. BAILEY, REDUCING RISKS TO LIFE at app. 35-45, 52-66 (1980).

71. Id. at app. 66 (Bailey's estimates are based on Thaler & Rosen, supra note 69; Blomquist, supra note 69; and Dillingham, supra note 69).

72. See Viscusi, Labor Market Valuations of Life and Limb: Empirical Evidence and Policy Implications, 26 Pub. Pol'y 359 (1978).

with reasonable estimates of the value of this risk reduction to determine if the regulation is likely to pass a benefit-cost test.

B. The Case Studies

Benzene, coke oven emissions, and acrylonitrile are all high-priority section 112 pollutants. Benzene has been listed formally⁷³ and regulations have been proposed,⁷⁴ and recently re-proposed, for several source categories.⁷⁵ Coke oven emissions and acrylonitrile are included in a list of thirty-seven substances the EPA is currently evaluating.⁷⁶ The health risks of and control options for these pollutants are well documented.⁷⁷ Although the following case studies use a common underlying methodology to estimate the benefits of controls for all three pollutants, the empirical details of the methodology vary considerably with each pollutant.

This section presents the results of benefit-cost analysis in each of the three case studies. The next sections suggest two approaches as alternatives to uniform BAT standards: (1) modification of the uniform standards to increase net benefits and (2) differential standards based on exposure levels around individual plants.⁷⁸

1. Maleic Anhydride (Benzene) Case Study⁷⁹

Maleic anhydride plants emit benzene, a major industrial chemical used in making nylon, plastics, insecticides and polyurethane foams. 80 A 1977 study by the National Institute of Occupational Safety and Health showed an abnormally high incidence of leukemia in workers exposed to benzene while employed at two plants in the rubber industry. 81 Following this study, the EPA listed benzene under section 112.82

^{73. 42} Fed. Reg. 29,332 (1977).

^{74. 45} Fed. Reg. 26,660 (1980).

^{75. 49} Fed. Reg. 8386 (1984).

^{76.} D. Patrick, supra note 50, app. on Section 112--The Process and Status.

^{77.} See, e.g., Office of Health & Envtl, Assessment, U.S. Envtl, Protection Agency, Health Assessment Document for Acrylonitrile (Mar. 1982) (draft) [hereinafter cited as Acrylonitrile Assessment Document].

^{78.} See infra notes 114-40 and accompanying text.

^{79.} Maleic anhydride plants convert benzene into maleic anhydride — a crystalline cyclic acid anhydride used chiefly in manufacturing resins and modified drying oils. The primary source of data for this case study is Benzene Emissions Background Information, supra note 58. For additional sources, see Nichols, supra note 42.

The analysis is based on data available to EPA when it proposed the standard for maleic anhydride plants in April 1980. Since then, however, several new developments have led EPA to propose the withdrawal of the proposed benzene control standards. See infra text accompanying notes 216–18.

^{80.} See S. Mara & S. Lee, Assessment of Human Exposure to Atmospheric Benzene 21 (May 1978) (report prepared by SRI International for U.S. Envtl. Protection Agency) [hereinafter cited as Human Exposure to Benzene].

^{81.} See Infante, Leukemia in Benzene Workers, 2 LANCET 76 (July 9, 1977). See also Nichols, supra note 42, at 149-50 (summarizing the studies of benzene's health effects).

^{82. 42} Fed. Reg. 29,332 (1977). After listing the pollutant, EPA commissioned studies

In April 1980, almost three years after listing benzene, EPA proposed an emission standard for maleic anhydride plants that use benzene as a feedstock.⁸³ The BAT standard called for an emissions reduction of roughly ninety-seven percent from uncontrolled levels.⁸⁴ A majority of the plants, however, already had installed controls of ninety percent or better, probably in response to state regulations directed at hydrocarbons or the hope that the benzene recovered would pay for the controls.85 As a result, the proposed BAT standard was expected to reduce full-capacity emissions by less than ninety percent, from 5.6 million kilograms per year to just under 0.5 million kilograms per year. 66

The costs of implementing the proposed standard were estimated at \$2.6 million per year in 1982 dollars. These costs are quite affordable to the maleic anhydride industry, whose total sales grossed \$142 million in 1979.88 The cost estimates are meaningless in isolation, however; they can be judged appropriately only in relation to the benefits they secure. As estimated, the proposed regulations would have reduced exposure by 3.6 million µg/m³-person-years and saved 0.4 lives annually.89

2. Coke Oven Emissions Case Study90

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Coke, produced by distilling coal in ovens, is essential to the production of iron and steel. In 1978, U.S. plants produced approximately

of benzene emissions. See PEDCo Environmental, Inc., Atmospheric Benzene Emisssions (Oct. 1977) (report submitted to U.S. EPA) (EPA-450/3-77-029) [hereinafter cited as Atmospheric Benzene Emissions]: S. Mara & S. Lee, Human Exposures to Atmospheric Benzene (Oct. 1977) (report prepared by Stanford Research Institute for U.S. EPA): Human Exposure to Benzene, supra note 80. These studies provided a rough idea of the relative amounts of pollution contributed by different types of sources. See also Nichols, supra

83. 45 Fed. Reg. 26,660 (1980). EPA developed an emission standard for maleic anhydride plants first, because more than half of all estimated emissions from chemical manufacturing plants came from the eight plants that used benzene to produce maleic anhydride. See Atmospheric Benzene Emissions, supra note 82, Table 1-2.

84. The standard limited existing plants to 0.3 kg of benzene emitted per 100 kg of benzene input. 45 Fed. Reg. 26,669 (1980).

85. See Benzene Emissions Background Information, supra note 58, Table 1-5.

86. 45 Fed. Reg. 26,660, 26,661 (1980).

87. Id. at 26,666. See also Benzene Emissions Background Information, supra note 58. For the two plants that had 90% controls, however, the cost estimates assume that they would need all-new control equipment; no credit is given for possible adaptation of existing controls. All of the cost estimates are for carbon absorption controls, which the EPA estimates indicated would be the lowest-cost control technique (including a credit for benzene recovered), and all assume 100% capacity utilization.

88. Facts and Figures for the Chemical Industry, CHEMICAL AND ENGINEERING News 26, 31 (June 13, 1982). The costs estimates included credits for the benzene recovered.

89. See Haigh, Harrison & Nichols, supra note 12, at 25-28.

90. The primary sources for the coke oven emission case study are: Emission Standards & Eng'g Div., Office of Air Quality Planning & Standards, U.S. Envtl. Protection Agency, Preamble and Regulation for Coke Oven Emissions from By-Product Coke Oven Charging, Door Leaks, and Topside Leaks on Wet-Coal Charged Batteries 1 (Mar. 1981)

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44 billion kilograms of coke.91 Epidemiological studies of coke-oven workers show that emissions from the coking process increased the risks of lung, trachea, bronchus, kidney, and prostate cancers. 22 Although the toxic elements include gases and respirable particulate matter, most attention has focused on the polycyclic organic matter (POM) contained in coal tar particulates. 93

Hazardous Air Pollutants

Coke oven emissions are released from numerous fugitive sources. including leaks and imperfections in the ovens. Charging emissions occur when coal is added to the ovens at the beginning of the coking process. Door leaks are the result of imperfect fits between the ovens and the doors through which the finished coke is later removed. Finally, imperfect seals on the lids and offtakes on the tops of the ovens create topside leaks.94

If the EPA listed coke oven emissions under section 112, the Agency would probably specify standards similar to the following as BAT: twelve percent of doors visibly leaking; three percent of lids visibly leaking and six percent of offtake systems visibly leaking; and sixteen seconds of visible emissions for each charging. 95 EPA estimates suggest that only thirty-seven of the fifty-four identified coke plants would have to increase control efforts to meet these standards (and some of those plants already meet one or two of the three potential BAT standards), * EPA estimates annual control costs for those plants at \$24.5 million. 97

Plant-specific emission estimates indicate that coke oven emissions would fall by 289,000 kg/year and exposure would fall by approximately

(draft) (Research Triangle Park, N.C.) thereinafter cited as 1981 EPA Draft Coke Oven Regulation]; Office of Air Quality Planning & Standards, U.S. Envtl. Protection Agency, Coke Oven Emissions from By-Product Coke Oven Charging, Door Leaks, and Topside Leaks on Wet-Coal Charged Batteries - Background Information for Proposed Standards (July 1981) (draft) (Research Triangle Park, N.C.) [hereinafter cited as 1981 Background Information]; Carcinogen Assessment Group, Office of Health and Envtl. Assessment, U.S. Envtl. Protection Agency, Carcinogen Assessment of Coke Oven Emission (Feb. 1982) (draft) (EPA-600/6-82-003) [hereinafter cited as EPA Coke Oven Assessment]; and Research Triangle Institute, Cost Estimates of Meeting the Potential EPA Regulation Affecting Coke Oven Emissions from By-Product Coke Oven Charging, Door Leaks, and Topside Leaks on Wet-Coal Charged Batteries (Apr. 1983) (computer printout) [hereinafter cited as 1983 Research Triangle Cost Estimate).

91. See 1981 Background Information, supra note 90, at 3-2.

92. See, e.g., EPA Coke Oven Assessment, supra note 90, at 108-12.

93. Id. at 54-63;

94. 1981 EPA Draft Coke Oven Regulation, supra note 90, at 4.

95. Id. at 4-5.

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96. A detailed breakdown of the status of individual plants is not available. The cost data supplied by the Research Triangle Institute, the primary EPA contractor for the coke oven analyses, includes positive entries only for those plants that are expected to require controls if standards are promulgated. Personal communication from Phillip Cooley of Research Triangle Institute (Aug. 1983).

97. 1983 Research Triangle Cost Estimate, supra note 90. EPA's emission and cost estimates are stated in terms of 1982 dollars and assume current compliance with existing state and OSHA regulations. Id.

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819,000 µg/m³-person-years if the above BAT standards were imposed.⁹⁸ Coke oven emissions are very potent carcinogens; this relatively slight reduction in exposure would save an estimated 10.6 lives each year.⁹⁹

3. Acrylonitrile Case Study100

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Acrylonitrile is an important industrial feedstock, employed primarily in the production of chemicals used to make a wide range of common products including rugs, clothing, plastic pipes, and automobile hoses. ¹⁰¹ Almost a billion kilograms of acrylonitrile were produced in 1981. ¹⁰² Extensive evidence indicating acrylonitrile's carcinogenicity exists. ¹⁰³ Specifically, epidemiological studies have associated acrylonitrile with respiratory cancers. ¹⁰⁴

While EPA has neither listed acrylonitrile nor proposed specific regulations, EPA contractors have identified available control options that could reduce emissions by at least ninety-five percent from uncontrolled levels. ¹⁰⁵ All thirty existing plants, however, already have implemented some type of controls. Thus, potential BAT standards would only cut annual emissions from 3.6 million kilograms to 0.5 million kilograms, a reduction of slightly less than eighty-seven percent. ¹⁰⁶ Uniform controls

98. Haigh, Harrison & Nichols, supra note 12, at 32-34.

99. EPA Coke Oven Assessment, supra note 90, at 144-63. See also infra Table 1.

101. Energy and Envtl. Analysis, Inc., supra note 100, at 3-1.

102. Facts and Figures for the Chemical Industry, CHEMICAL AND ENGINEERING

News 30, 37 (June 14, 1982).

103. EPA identified three epidemiological studies; seven lifetime laboratory studies with rats; several mutagenicity studies with bacteria, Drosophila (fruit flies), and rodents; chromosomal studies of humans; and numerous metabolic studies. Carcinogen Assessment Group, Office of Health & Envtl. Assessment, U.S. Envtl. Protection Agency, Health Assessment Document for Acryolnitrile 101 (1982).

104. See EPA Acrylonitrile Assessment, supra note 100, at 1, 63-67.

105. See Key & Hobbs, supra note 100, ch. V, at 1-4, ch. VII, at 1-3 (discussing such control systems).

106. These calculations of emission reductions are based on "current" emissions in

would create an estimated annual expense of almost \$29 million in 1982 dollars. 107 Reduced exposure to acrylonitrile, just over 450,000 µg/m³-person-years, would avoid only one case of cancer every five years (0.2 lives per year). 102

C. Analysis of the Best Available Technology Standards

Table 1 summarizes the results of the BAT standards analyzed. Controls on coke oven emissions produce much greater health benefits than do controls on the emissions of benzene or acrylonitrile. BAT controls on coke ovens would result in almost eleven fewer cases of cancer each year, compared to reductions of 0.4 cancer deaths for maleic anhydride benzene controls and 0.2 cancer deaths for acrylonitrile standards.

The final line of Table 1 presents the most relevant figure in measuring the cost-effectiveness of the three control standards — the value placed on saving a life that is necessary to justify incurring control costs. To justify acrylonitrile controls on benefit-cost grounds, the value of a statistical life would have to be at least \$144 million, an implausible figure from virtually any perspective. ¹⁰⁹ The cost-effectiveness figure for benzene, \$6.5 million, also is larger than the range of plausible estimates. Controls on coke oven emissions are the most attractive of the three BAT options. To justify the coke oven emissions standards on benefit-cost grounds, the value of a life saved must be equal to or greater than \$2.3 million. That value does fall within the range of the published benefit estimates. Nevertheless, all three BAT options would fail a conventional benefit-cost test based upon a value of \$1 million per life saved.

Table 2 indicates two principal reasons why the cost-effectiveness of control varies so greatly among the pollutants. First, the carcinogenic potency of coke oven emissions is much greater than for acrylonitrile or for benzene. 110 Second, coke oven emissions affect many more people than do the other pollutants. Fugitive coke emissions occur at ground

109. See supra notes 67-72 and accompanying text.

^{100.} The acrylonitrile case study relied on data assembled from several sources, including Click & Moore, Emission, Process and Control Technology Study of the ABS/ SAN Acrylic Fiber, and NBR Industries (Apr. 1979) (report prepared by Pullman Kellogg for the Office of Air Quality Planning & Standards, U.S. EPA, contract 68-02-2619); Key & Hobbs, Acrylonitrile (Nov. 1980) (report prepared by IT Enviroscience for the Office of Air Quality Planning & Standards, U.S. EPA); Energy & Envtl. Analysis, Inc., Source Category Survey for the Acrylonitrile Industry (July 1981) (draft report prepared for the Office of Air Quality Planning & Standards, U.S. EPA, under contract 68-02-3061); Radian Corporation, Locating and Estimating Air Emissions from Sources of Acrylonitrile (Dec. 1982) (draft report prepared for Office of Air Quality Planning & Standards, U.S. EPA); Carcinogen Assessment Group, Office of Health & Envtl. Assessment, U.S. Envtl. Protection Agency, The Carcinogen Assessment Group's Carcinogen Assessment of Acrylonitrile (Feb. 1982) (draft) [hereinafter cited as EPA Acrylonitrile Assessment]; B. Suta, Assessment of Human Exposure to Atmospheric Acrylonitrile (Aug. 1979) (report prepared by SRI Int'l for U.S. EPA) [hereinafter cited as 1979 Assessment of Exposure to Acrylonitrilel; B. Suta, Revised Assessment of Human Exposure to Atmospheric Acrylonitrile Using Industry Supplied Emission Estimates (1982) (report prepared by SRI Int'l for U.S. EPA); and personal correspondence from B. Suta (Aug. 1982) (data on exposure to acrylonitrile emissions) [hereinafter cited as Suta Data on Acrylonitrile].

U.S. Envtl. Protection Agency, Summary of Acrylonitrile Emission Estimates and Production Capacities (Jan. 1983) (draft) (tables provided by R. Crume, Office of Air Quality Planning & Standards), and on model-plant controlled emissions in Key & Hobbs, supra note 100, ch. V, at 1-4 for AN monomer and in Click & Moore, supra note 100, at 61-64. See also Haigh, Harrison & Nichols, supra note 12, at 36-38.

^{107.} The control costs are estimated from model plant data in Key & Hobbs, supra note 100, at Table VI-2, and new plant data in Energy and Envtl. Analysis, Inc., supra note 100, at Table 5-5 for AN monomer and in Click & Moore, supra note 100, at Table 6-1, for the other categories. All costs have been updated to 1982 dollars using the GNP implicit price deflator. See also Haigh, Harrison & Nichols, supra note 12, at 36-38 and Table 2.11.

^{108.} See Haigh, Harrison & Nichols, supra note 12, at 36-41. Exposure factors were estimated using dispersion modeling results and plant-specific population data provided in Suta Data on Acrylonitrile, supra note 100.

^{110.} See infra Table 2 (indicating carcinogenic potency with unit risk factors). See also supra notes 64-66 and accompanying text,

Table 1: Benefits and Costs of BAT Standards

| | Benzene [®] | Coke Ovens | Acrylo- nitrile |
|--------------------------------|----------------------|---------------|--------------------|
| Annual Costs and Benefits | | | |
| Control Cost (\$1000) | 2,577 | 24,511 | 28,988 |
| Number of plants | 8 | 37 | 31 |
| Reduced Emissions (1000 kg) | 5,059 | 289 | 3,112 |
| Reduced Exposure (1000 µg/ | • | | |
| m³-person-yrs) ^b | 3,646 | 819 | 455 |
| Lives Saved ^c | 0.4 | 10.6 | 0.2 |
| Cost-Effectiveness | | | |
| Emissions (\$/kg) | 0.51 | 84.8 | 9.3 |
| Exposure (\$/µg/m³-yr) | 0.71 | 29.9 | 63.7 |
| Lives saved (\$1 million/life) | 6.5 | 2.3 | 144. |

a. Estimates are based upon the 1980 proposed standard for maleic anhydride plants.

b. Exposure reductions are calculated by aggregating the concentration changes for people at different distances from each plant. For example, if 1000 people have their exposure reduced by 10 micrograms per cubic meter (µg/m³) in a given year, exposure would be reduced by 10,000 μg/m³-person-years.

c. Lives saved are calculated by multiplying the exposure reduction by a unit risk factor that measures the increased probability of contracting cancer as a result of exposure to 1 μg/m³ for one year. For example, if exposure is reduced by 1000,000 μg/m³-per-years for a carcinogen that increases the risk of cancer by 1.5 × 10⁻⁴ for each µg/m³-per-year, a total of 15 statistical lives would be saved. (Note: this article assumes that all cancer cases result in premature death.)

level rather than from stacks, and coke plants tend to be located closer to large population concentrations.¹¹¹ As a result, a kilogram of coke oven emissions causes three times the exposure that a kilogram of benzene emitted from maleic anhydride plants does and over seventeen times the exposure that a kilogram of acrylonitrile does. 112 Because of these two factors, a reduction of one kilogram in coke oven emissions produces a risk reduction roughly 500 times greater than for either of the other cases.113

Together, tables 1 and 2 indicate that concentrating only on the cost per kilogram of emission reduction provides a misleading measure of the relative attractiveness of the three BAT standards. A kilogram of coke oven emissions is much more costly to control than a kilogram of either acrylonitrile or benzene. The marginal benefit of controlling coke oven emissions is so much larger, however, that coke ovens are far more costeffective objects of regulation. This comparison gives the most compel-

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Table 2: Risk and Exposure Information for the Three Cases

| - | Benzene* | Coke Oven Emissions | Acrylonitrile |
|---|------------------------|---------------------------|------------------------|
| Unit risk factor (deaths/ µg/m³-yr) ^b | 1.1×10^{-7} | 1.3 × 10 ⁻⁵ | 4.4 × 10 ⁻⁷ |
| Total population exposed ^c | 8,080,000 | 25,948,000 | 8,457,000 |
| Population within 1 km Average exposure factor | 27,550 | 90,193 | 7,138 |
| (μg/m³-person-yrs/kg) ^d | 0.721 | 2.83 3.7 × | 0.146 |
| Risk per kg of emissions | 7.9 × 10 ⁻⁸ | 10-5 | 6.4×10^{-8} |

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a. Estimates are based upon the 1980 proposed standard for maleic anhydride plants.

b. See footnote c. Table 1.

c. Population within 20 km of all plants.

d. The exposure factor is calculated by dividing the reduced exposure by the reduced emissions. For example, the calculation for coke oven emissions is: 819,000 µg/m³ personyears divided by 289,000 kg, which equals 2.83.

ling reason for formally evaluating the benefits of toxics control. It is impossible to target controls where they provide the greatest health benefits without considering relative carcinogenicity and relative exposure factors.

D. Analysis of Alternate Standards

Benefit-cost criteria assist policymakers in evaluating regulatory alternatives beyond uniform BAT standards as well. This section analyzes two alternatives for each pollutant: (1) a relaxed uniform standard; and (2) a set of differential standards that would be more stringent for plants located in more densely populated areas than for plants that cause less exposure.

Choosing the appropriate degree of control is a common issue in pollution regulation. 114 Controls should be tightened as long as the marginal benefits exceed the marginal costs. Negative net benefits at one control level do not imply that regulation is undesirable at all levels, because a less stringent alternative may provide positive net benefits.

Pollution control regulations can also be targeted to specific firms. 115 The EPA and other regulatory agencies typically develop regulations for

^{111.} See infra Table 2 (comparing population figures across the three case studies).

^{112.} Id. (comparing average exposure factors across the three case-study pollutants).

^{113.} Id. (comparing risk per kilogram of emissions across the three case-study

^{114.} E. STOKEY & R. ZECKHAUSER, A PRIMER FOR POLICY ANALYSIS 139-42 (1978). 115. See Harrison & Nichols, Benefit-Based Flexibility in Environmental Regulation (Apr. 1983) (Discussion Paper Series, Kennedy School of Government, Harvard University) (discussing the general advantages of these differential standards and an evaluation of potential obstacles). The potential policy considerations that might arise in imposing different standards on different plants, including equal protection issues and problems arising from regulations that encourage businesses to locate new plants in less populated but generally more pristine areas, lie beyond the scope of this article.

to \$28.8 million for the BAT standards for acrylonitrile plants.

Table 3: Benefits for Alternative Strategies

| | | Benzene* | Coke Ovens | Acrylonitrile |
|------------------------------------|--------------|----------|------------|---------------|
| Percentage of BAT Resu | dts | | | |
| Relaxed Uniform Stan | | | | |
| Benefits | | 94 | 80 | 62 |
| Costs | • | 57 | 61 | 29 |
| Differential Standard ^c | | | | |
| Benefits | | 96 | 81 | 60 |
| Costs | • | 37 | 33 | 18 |
| Cost per Life Saved (in ; | \$1 million) | | | |
| Relaxed Uniform ^b | | 3.9 | 1.8 | 64.2 |
| incremental BAT | | 41.6 | 4.7 | 274. |
| Differential ^c | | 2.5 | 0.93 | 42.1 |
| incremental BAT | | 80.4 | 8.3 | 286. |
| Net Benefits (\$ million/y | ear) | | | |
| BAT | | -2.2 | -13.9 | -28.8 |
| Relaxed uniform | | -1.1 | -6.4 | -8.0 |
| Differential | | -0.6 | 0.5 | -4.9 |

a. Estimates are based on data available to EPA when the standard was proposed.

b. Defined as:

maleic anhydride: 90 percent

coke ovens: doors only

acrylonitrile: AN monomer and nitrile elastomer plants

c. Defined as:

maleic anhydride: 97 percent control for plants with exposure factors greater than

coke ovens; doors and topside for plants with factors greater than 2.0 acrylonitrile: BAT controls for AN monomer and nitrile elastomer plants with exposure factors greater than 0.2

broad source categories. Section 112 is typical; the BAT standards apply to all plants within the source category. This approach ignores the fact that plants located in high density areas affect many more people and produce much greater exposure reduction for the same amount of emission control.116

Table 3 summarizes the application of these alternate regulatory strategies to the three pollutants. Alternatives that target controls on the high-exposure plants are referred to as "differential standards." Both the relaxed standards and the differential standards reduce costs much more than they reduce benefits. The cost-per-life-saved estimates, however, are still quite high. In fact, the only alternative that yields positive net benefits at a value per life saved of \$1 million is differential standards for coke oven emissions. The other alternatives result in net losses ranging

The wide range in net benefits demonstrates the need for more detailed analysis of alternative regulatory strategies for the specific pol-

lutants. In addition, the details of estimating the benefits and costs of alternatives differ considerably among specific pollutants. Since the analysis of the effect of uncertainty presumes a familiarity with the derivation of the estimates, a more comprehensive description of the case study results is presented below.

1. Benzene

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Of the five maleic anhydride plants that would need new control equipment to meet a ninety-seven percent control standard, two already achieve ninety percent control. 117 Therefore, the marginal cost of increasing control efficiency in these plants by seven percent is quite high. EPA would save a substantial amount of money with little change in benefits by relaxing the standard to a ninety percent control level. The estimated exposure reduction is only six percent lower than at ninety-seven percent. but costs fall forty-three percent. 118 The cost per statistical life saved drops to \$3.9 million, a substantial improvement over the BAT proposal. The cost per statistical life saved of BAT standards rises to \$41.6 million when ninety-seven percent controls are compared to ninety percent controls. Therefore, unless the value of a statistical life saved is taken as greater than \$41.6 million, the stricter standard is unjustified. 119

A uniform standard of ninety percent control improves cost-effectiveness by screening out plants for which the proposed standard has little impact on emissions or exposure. Differential standards, which set tighter requirements for plants with high exposure factors, offer a more ambitious and controversial way of increasing efficiency. 120 In extreme form, differential standards based on exposure factors lead to plantspecific standards. Limited categorization is a more practical approach. The eight plants emitting benzene, for example, could be split into four "high-exposure" plants and four "low-exposure" plants. 121 A regulation requiring ninety-seven percent controls on only the high-exposure plants, and no additional controls on the other plants, yields ninety-six percent of the benefits of the proposed uniform standard at thirty-seven percent of its cost. 122 The differential standard also surpasses the uniform ninety

^{116.} The maleic anhydride plant located in St. Louis, for example, accounts for approximately 80% of the overall benefits. See Haigh, Harrison & Nichols, supra note 12,

^{117.} See Benzene Emissions Background Information, supra note 58, at Table 1-5.

^{118.} See Haigh, Harrison & Nichols, supra note 12, at 28-29. Unfortunately, the EPA has not developed cost estimates for 90% controls. A conservative estimate of the net benefits of relaxing the standard results from assuming that 90% controls would cost just as much as those achieving 97% for the three plants that currently have no controls.

^{120.} See generally Harrison & Nichols, supra note 115 (discussing the advantages of varying standards in response to inter-plant differences in the marginal benefits of emission control).

^{121.} See Haigh, Harrison & Nichols, supra note 12, at 29-30.

^{122.} Id.

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mer, and ABS/SAN resin plants. 132 The cost-effectiveness estimates vary

widely among these source categories. A regulation restricting the BAT

standards to the two most cost-effective source categories, the nitrile

percent alternative, achieving slightly greater benefits at seventy-one percent of the cost.¹²³ Thus, even a crude, two-level differential standard significantly improves the cost-effectiveness of benzene standards.¹²⁴

2. Coke Oven Emissions

The EPA could improve the cost-effectiveness of BAT controls on coke oven emissions by eliminating controls on some sources of emissions. ¹²⁵ Controls on charging are substantially less cost-effective than those for doors or topside leaks. ¹²⁶ Eliminating the charging standard reduces costs by twenty-nine percent, but cuts benefits by only nine percent. Controls on door leaks are the most cost-effective component of the BAT standard, with a cost-effectiveness ratio of less than \$1.8 million per statistical life saved. By imposing BAT standards solely on door leaks, the EPA would cut costs thirty-nine percent while retaining eighty percent of the benefits of the complete BAT standard. ¹²⁷

A total of fifty-four plants would be subject to BAT control requirements, but seventeen plants currently meet the requirements. 128 The exposure to coke oven emissions varies widely across the remaining thirty-seven plants, with the exposure factor ranging from a low of 0.58 to a high of 5.93. 129 The wide range in exposure factors offers an opportunity to increase efficiency by restricting the standard — or portions of it — to plants with relatively high exposure factors. Of the thirty-seven plants, twenty-one have exposure factors greater than 2.0 µg/m³-person-years/kg. 130 A regulation imposing the door and topside standards only on those plants yields eighty-one percent of the benefits at only thirty-three percent of the cost of the uniform BAT standard. 131

3. Acrylonitrile

The thirty plants currently emitting acrylonitrile can be divided into four source categories: AN Monomer, acrylic fiber plants, nitrile elasto-

elastomer and AN monomer plants, would yield sixty-two percent of the benefits of the complete set of standards at twenty-nine percent of the cost. 133 The average cost per life saved, however, would still be over \$64 million. 134 Controls on even the most cost-effective category, nitrile elastomer plants, yield a cost per life saved of almost \$48 million. Thus, none of the BAT standards for controlling acrylonitrile emissions can be justified on benefit-cost grounds.

EPA model plant data indicate that a flare to control column-vent emissions from AN monomer plants would reduce emissions about seventy-six percent below uncontrolled levels at a cost of less than \$0.032 per kilogram of acrylonitrile. 135 Using the average exposure factor for

those plants of 0.248 µg/m³-person-years/kg, the implicit cost per life saved would be under \$290,000, a relatively modest sum.¹³⁶ All of the AN monomer plants, however, already have such flares.¹³⁷ This fact affords at least one indication that manufacturers have already installed those control devices that are least expensive.

As in the other two case studies, widely varying exposure factors offer opportunities to improve cost-effectiveness by limiting standards to high-exposure plants. ¹³⁸ Regulations restricting BAT standards to AN monomer and nitrile elastomer plants with exposure factors greater than 0.2 µg/m³-person-years/kg, for example, yield sixty percent of the benefits of the complete set of BAT standards at only eighteen percent of the cost. ¹³⁹ The most cost-effective plant, however, has a cost-effectiveness ratio of approximately \$18 million per life saved. ¹⁴⁰ Thus, although

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Plants in the last three categories all use AN monomer as a feedstock. The largest feedstock use is acrylic fibers, employed primarily to manufacture rugs and clothing. ABS and SAN are toth resins used to produce hard plastics for such items as pipes, appliances, disposable utensils, and packaging. Nitrile elastomer is a type of rubber used extensively in the automobile industry for hoses, gaskets, and seals.

Id. at 17-18. See also Energy and Envtl. Analysis, Inc., supra note 100, at 1-1 to 1-9.

^{123.} Id.

^{124.} Of course, the cost-effectiveness of the differential standards will vary with the categorization of the "high exposure" plants. Id. at 31.

^{125.} Although the data available to the EPA permit consideration of the individual components of the BAT standard for coke oven emissions, it is insufficient to analyze alternative levels for the different sources within plants.

^{126.} See Haigh, Harrison & Nichols, supra note 12, at 34-35.

^{127.} Id. The door standard still does not yield positive net benefits, however, unless the value ascribed to saving a life is at least \$1.8 million (based again on the CAG risk estimate). Id.

^{128.} See id. at 16 (citing U.S. EPA, Draft Tables on Maximum and Minimum Emission Estimates from By-Product Coke Oven Charging, Door Leaks, and Topside Leaks on Wet-Coal Charged Batteries (Apr. 1983)).

^{129.} See id. at 33 (citing 1981 Background Information, supra note 90, at app. E).

^{130.} See 1983 Research Triangle Cost Estimate, supra note 90.

^{131.} See Haigh, Harrison & Nichols, supra note 12, at 35-36.

^{133.} See Haigh, Harrison & Nichols, supra note 12, at 39-40.

^{134.} Id.

^{135.} See Key & Hobbs, supra note 100, Table VI-2.

^{136.} See Haigh, Harrison & Nichols, supra note 12, at 39-40.

^{137.} See Key & Hobbs, supra note 100, at app. F, at Table F-1.

^{138.} Another possibility is to consider less stringent regulations for the individual source categories. The EPA, however, has not analyzed such alternatives.

^{139.} See Haigh, Harrison & Nichols, supra note 12, at 40-41. The estimated reduction in emissions from controlling those plants is 312,000 µg/m³-person-years, while the estimated control cost is \$8.4 million.

^{140.} Id. The estimated reduction in exposure from controlling that plant is 98,000 µg/m'-person-years, while the estimated cost is \$800,000.

differential standards substantially improve the cost-effectiveness ratios of acrylonitrile controls, they do not yield benefits commensurate with the costs of control.

E. Summary

The results of the three case studies indicate that uniform technology-based controls have vastly different net benefits depending upon the pollutant and the source category. The implicit cost per life saved by BAT standards varies by a factor of almost 100 among the three pollutants. Moreover, in each of the three cases, alternate standards yield higher net benefits than BAT for any plausible value of risk reduction. For two of the three cases, however, even the most cost-effective standards considered fail any reasonable benefit-cost test. In the third case, coke oven emissions, regulation produces positive net benefits for a value per life saved of \$1 million only by relaxing the control standard and restricting it to high-exposure plants.

These conclusions must be viewed as tentative, for they do not take into account the substantial uncertainties associated with estimating the benefits of controlling airborne carcinogens.

III. Uncertainties in Estimating Benefits

The benefit estimates discussed in the case studies employ point estimates of parameter values based on EPA data. Most of the estimates, however, are highly uncertain; the plausible range for the unit risk estimate in each case covers several orders of magnitude. Critics argue that such uncertainties render quantitative analysis too unreliable to guide policy. The key issue, however, is not whether the estimates are precise—clearly they are not—but how robust the conclusions are in the face of substantial uncertainties and potential errors. This Part evaluates each of the four steps in benefit estimation, beginning with the estimation of emission reduction. It addresses both the generic problems and specific examples from the case studies for each step. Additionally, it considers the potential importance of non-cancer control benefits that have not been quantified.

A. Uncertainties in Estimating Emissions

In theory, estimating emission reductions involves nothing more than monitoring the pollutant source before and after control, and subtracting the results. Despite this apparent simplicity, estimates of the reduction in emissions are far from precise. Several sources of uncertainty, common to the vast majority of regulations likely to be considered under section 112, arise in measuring emissions. In the case of coke oven controls, emissions estimation may be the largest source of uncertainty in estimating the benefits of regulation.

The uncertainties in estimating emissions and emission reductions are particularly great at the level of individual plants. The EPA bases its emission estimates on a model plant and projects them to actual individual sources using a limited number of plant-specific factors. ¹⁴¹ In each of the three cases, for example, EPA assumed that all plants within a given category had the same uncontrolled emission rate. In reality, however, plants are likely to vary widely. An EPA contractor estimated that maleic anhydride plants vary by a factor of three in the amount of benzene that is not converted in the manufacturing process, and that would thus be emitted in the absence of controls. ¹⁴² Nitrile elastomer plants emitting acrylonitrile show a similar range. ¹⁴³

Another factor creating uncertainty in model plant projections is the lack of adequate knowledge about the effectiveness of existing controls. Although many plants already have emission controls of some kind, due to state regulations, Occupational Safety and Health Administration (OSHA) standards, or economic self-interest in recovering valuable feedstock or by-products, the EPA has made only rough estimates of the effectiveness of such controls.¹⁴⁴

Finally, model plant estimates do not consider the effects of varying production levels on eventual emissions. Emissions depend on both the emission rate and the percentage of plant capacity used. 145 Few plants operate at full capacity; thus, benefit estimates must be adjusted downward to compensate for actual production levels. This problem is most severe when control techniques are capital-intensive because control costs are then fixed across all production levels while benefits vary directly with production levels. 146 Therefore, the EPA model plant projections may be highly inaccurate predicters of emission reductions at actual plants.

Even if emission estimates are accurate at the time they are made, they may not provide reliable projections of the impact of a proposed regulation. The effects are most dramatic in the case of maleic anhydride plants, where all of the uncontrolled plants identified by EPA when the regulation was proposed have since closed, switched feedstocks, or installed controls.¹⁴⁷ In the case of coke ovens, the depressed state of the

^{141.} See Nichols, supra note 42, at 184-86.

^{142.} Benzene Emissions Background Information, supra note 58, at 1-7. See also, Nichols, supra note 42, at 181.

^{143.} See Radian Corporation supra note 100, at 43.

^{144.} See, e.g., Benzene Emissions Background Information, supra note 58, at Table 1-5 (presenting estimates of current benzene emissions from maleic anhydride plants).

^{145.} Obviously, as capacity utilization declines the production process uses less of the substance and therefore emits less of it.

^{146.} Benefits are proportional to the amount of emissions reduced and the emission reduction is related to the production level. Hence, if production levels drop, so do total benefits. Because capital costs are fixed, the benefit-cost ratio also drops.

^{147.} See infra notes 216-218 and accompanying text.

steel industry suggests that additional plants may close over the next few years. 148

Emission estimates are likely to be most uncertain when each plant has multiple "fugitive" sources (such as leaking doors), as the coke oven case illustrates. An EPA contractor presented minimum and maximum estimates, which vary by a factor of 11 for door leaks, 6.4 for topside leaks and over 300 for charging leaks. ¹⁴⁹ The results for coke ovens presented in Part II use a simple average of the minimum and maximum estimates. ¹⁵⁰ Substitution of the maximum estimates reduces the cost per life saved by less than a factor of two. Use of the minimum estimates, however, increases the cost per life saved by more than a factor of six for the BAT standard. ¹⁵¹

Uncertainties about emissions appear to be most important for coke ovens because: (1) the uncertainties are much greater for coke ovens than for either of the other cases; and (2) the coke oven decision is the "closest" one, with cost-effectiveness ratios in the plausible range. Even with the maximum emission estimates, however, it is not clear that the uniform BAT standard yields positive net benefits.

These results suggest that it would be useful to narrow the range of estimates of emissions from coke ovens, particularly if the tentative decision was to proceed with regulation. A plausible benefit-cost case for the BAT standard is possible only if actual emissions are in the upper end of the estimated range.

2. Uncertainties in Estimating Exposure

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The dispersion models used by the EPA to predict pollutant exposure contain pervasive uncertainties. In particular, critics question the reliability of these models at substantial distances from sources and their ability to predict concentrations indoors, where individuals spend most of their time.

Dispersion models for toxic air pollutants combine source characteristics, like the height and velocity of releases, with meteorological inputs, including wind speed, direction, and turbulence. Statistically the methodology is straightforward, the accuracy of these dispersion models is uncertain. Model accuracy is difficult to evaluate empirically because, in many cases, measured ambient concentrations at a particular location

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The accuracy of the models detailed and sources modeled.

The accuracy of the models deteriorates as the distance from the source increases.¹⁵⁴ As a result, dispersion modeling usually is not carried out more than thirty kilometers from the source plant.¹⁵⁵ In theory this truncation introduces a bias, understating total exposure levels. Concentrations at greater distances, however, are typically very low, making the resulting bias very minor as well.¹⁵⁶

Dispersion models are designed to predict outdoor concentrations, but most people spend the vast majority of their time indoors. Recent studies of "indoor air pollution" suggest that concentrations of pollutants indoors may be very different from those outdoors. 157 Many of these studies, however, have involved pollutants that have indoor as well as outdoor sources. 158 Pollutants emitted solely by outdoor sources will have equal or *lower* average concentrations indoors than those outdoors. 159 Therefore, the use of outdoor concentrations to estimate exposure levels may overstate the benefits of the regulations.

Another source of uncertainty arises from the failure to use plant-specific data in estimating exposure from individual plants. Exposure levels around a particular plant critically depend on whether prevailing winds blow toward or away from densely populated areas. Variables like stack height, exit velocity, gas temperature and local meteorological data also affect actual exposure. 160 None of the case studies, however, used such plant-specific data to calculate exposure factors. 161

^{148.} See U.S. Envil. Protection Agency, Draft Tables on Maximum and Minimum Emission Estimates from By-Product Coke Oven Charging, Door Leaks, and Topside Leaks on Wet-Coal Charged Batteries (Apr. 1983) (provided by S. Grove, Office of Air Quality Planning & Standards).

^{149.} See, e.g., 1981 EPA Draft Coke Oven Regulation, supra note 90, at 1. The charging standard under consideration for coke ovens, for example, sets an upper bound on the number of seconds of visible emissions during the charging cycle. Id.

^{150.} See supra notes 90-99, 125-131 and accompanying text.

^{151.} See Haigh, Harrison & Nichols, supra note 12, at 61.

^{1&#}x27; e Benzene Emissions Background Information, supra note 58, at 4-11 to 4-17.

^{153.} C. Miller, Exposure Assessment Modeling: A State-of-the-Art Review (1978) (report prepared for U.S. EPA) (EPA-600/3-78-065).

^{154:} See Haigh, Harrison & Nichols, supra note 12, at 62-63.

^{155.} See, e.g., 1979 Assessment of Exposure to Acrylonitrile, supra note 100, at Table VI-5; Benzene Emissions Background Information, supra note 43, at app. E-8. The modeling for maleic anhydride plants was carried out only to 20 kilometers, which may distort comparisons with the other cases. Id. To check for possible bias, exposures for coke ovens and acrylonitrile were estimated using data carried out to only 20 kilometers and the results were compared with the original estimates. The comparisons were reassuring: the differences were only 9% for coke ovens and 11% for the acrylonitrile plants. See Haigh, Harrison & Nichols, supra note 12, at 63.

^{156.} See, e.g., 1979 Assessment of Exposure to Acrylonitrile, supra note 100, at Table VI-5.

^{157.} See, e.g., Spengler & Sexton, Indoor Air Pollution: A Public Health Perspective, 221 Science 9 (July 1983) (compiling the various primary studies on indoor air pollutants).

^{158.} Id. at 11.

^{159.} Id.

^{160.} Greater accuracy could be achieved by using more plant-specific parameters, some of which could be measured with very low decision costs. It would seem particularly easy and cost-effective, for example, to use local meteorological data.

^{161.} See 1981 Background Information supra note 90, at app. E (extrapolating from Pittsburgh meterological data to all coke oven plants); Benzene Emissions Background Information, supra note 58, at app. E, at E-8 (extrapolating from Pittsburgh meterological data to all maleic anhydride plants); 1979 Assessment of Exposure to Acrylonitrile, supra note 100, at 26 (basing acrylonitrile results on generalized conditions rather than actual data from any particular area).

Finally, EPA estimates implicitly assume that individuals spend all of their time close to their homes; the population data are based on place of residence. This assumption is accurate for children who attend nearby schools, or for non-working adults who spend most of their time at or near home. It may, however, create larger inaccuracies for adults who work far from their homes. To the extent that concentrations where people work are different from those at home, the exposure factors will be inaccurate. Plants located in areas where more people work than live create higher than estimated exposure levels, but the opposite occurs if plants are located in areas where more people live than work.

Uncertainties about the exposure factors used in these case studies have not been quantified. The uncertainties are greatest, however, at the level of individual plants, because of the failure to use plant-specific values for any parameters other than population. No systematic sources of upward or downward bias are apparent in the case study exposure estimates.

. C. Uncertainties in Estimating Risk

Estimating the unit risk factor is the most uncertain step in analyzing carcinogens. Evidence of carcinogenicity typically comes from either high-dose animal studies or from epidemiological studies of workers exposed to relatively high concentrations of the substance. All three of the case studies described above relied on epidemiological evidence of carcinogenicity as the primary basis for risk assessment. ¹⁶⁴ Thus, none involves the difficult and controversial task of extrapolating carcinogenicity from animals to humans. ¹⁶⁵ Risk estimates in the case studies did, however, require substantial extrapolation from high-dose to low-dose exposure. ¹⁶⁶

The problem of extrapolating from high-dose data to low-dose exposures arises because neither epidemiological studies nor laboratory experiments with animals are capable of detecting low-level risks. 167 Several mathematical models have been developed to perform the necessary extrapolations. 168 Unfortunately, neither current theory nor empirical evidence provides unambiguous support for any one model. 169

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Most regulatory agencies, including the EPA, use the "one-hit" model or a variant of it.¹⁷⁰ That model assumes that cancer can be induced by a single "hit" of a susceptible cell by a carcinogen. Thus, the model does not yield a threshold below which there is a zero risk of cancer. At low exposure levels, the predicted risk is proportional to the dose; if the relevant dose is 1000 times lower than that at which the risk was measured, for example, the estimated risk is also 1000 times lower. Because, of this property, the "one-hit" model is often called the "linear" model.

It is difficult to tell how much of the linear model's popularity is due to scientific belief in its accuracy as opposed to a value judgment that decisionmakers should be conservative in the face of great uncertainty. In any event, most scientists accept the linear model as providing an upper-bound estimate of cancer risk.¹⁷¹

The other models commonly used in estimating cancer risk are convex at low doses; as the dose is reduced, risk falls more than proportionately.¹⁷² Given the same data, these models all predict smaller low-dose risks than the linear model.¹⁷³ In fact, when the extrapolation from measured risk covers two or more orders of magnitude, as typically happens in EPA regulation, the other models' estimates may be treated as zero because they are so much lower than the linear model's projections.¹⁷⁴ Thus, regulations to reduce low dose exposure to environmental carcinogens must rest on a belief that the linear model has a significant probability of being correct.

Ideally, experts could assess the probability that each of the possible models is correct, and then use those probabilities to compute an expected dose-response function. Unfortunately, such assessments are not available. If they were, it is likely that the expected dose-response function would be approximately linear at low doses, because the nonlinear models predict such small risks that the linear model component would dominate so long as the probability assigned to the linear model's correctness was nontrivial. Note, however, that the unit risk factor for the expected dose-response function would not be as large as that estimated by the linear model alone; the estimated risk would equal approximately the pure linear estimate times the probability that the linear model is correct. Thus, while it may be reasonable to assume that the expected benefits of control are proportional to the reduction in exposure, estimates of reduced mortality in this article are probably too high, perhaps

^{162.} See, e.g., Benzene Emissions Background Information, supra note 58, at app. E, at E-6.

^{163.} See supra notes 152-62 and accompanying text. See also Harrison, Distributional Objectives in Health and Safety Regulation, in The Benefits of Health and Safety Regulation in The Benefits of Health and Safety Regulation 177-201 (A. Ferguson & E. LeVeen eds. 1981) (estimating exposure to automotive air pollution at work as well as at home).

^{164.} See supra note 81 and accompanying text (benzene). See supra note 92 and accompanying text (coke ovens). See supra note 103 and accompanying text (acrylonitrile).

^{165.} See E. CROUCH & R. WILSON, RISK/BENEFIT ANALYSIS 64-68 (1982).

^{166.} These studies often measured risk, however, at doses 1000 or more times higher than the exposure levels affected by the regulation. *Id.* at 114-16.

^{167.} *İd*.

^{168.} See Nichols, supra note 42, at 164-70 (discussing the various models).

^{169.} *Id*

^{170.} See, e.g., E. CROUCH AND R. WILSON, supra note 165, at 115.

^{171.} In its preliminary report on benzene, for example, the CAG said that the linear model "is expected to give an upper limit to the estimated risk." See Carcinogen Assessment Group, Office of Health & Envtl. Assessment, U.S. Envtl. Protection Agency, Carcinogen Assessment Group's Preliminary Report on Population Risk to Ambient Benzene Exposures 1 (1977) (unpublished paper).

^{172.} See Nichols, supra note 42, at 164-70.

^{173.} See id. (providing equations for the various models and an example of their widely different predictions at low doses when estimated from the same high-dose data), 174. See id, fig. 7.2, at 168.

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by a substantial margin, because they rely exclusively on the linear model.

Even if one accepts the linear model, controversies about the interpretation of epidemiological data make the unit risk estimates uncertain. Exposure levels in epidemiological studies often cause the greatest difficulties because the exposures typically occurred many years earlier when few measurements were made.¹⁷⁵ The controversy surrounding the CAG's risk estimate for benzene illustrates this problem and others that can arise in interpreting epidemiological studies.¹⁷⁶

The CAG based its unit risk estimate for benzene on data from three epidemiological studies.¹⁷⁷ In each case, it had to make assumptions about exposure and other factors. Many of these assumptions have been criticized for overstating the risk.¹⁷⁸ Two EPA analysts, for example, concluded that the CAG risk estimate was too high by a factor of four.¹⁷⁹ An occupational physician testified that the CAG estimate should have been lower by more than a factor of ten.¹⁸⁰ The differences between these estimates and the CAG's are particularly startling because they were based on the same studies and model.

Disputes about the appropriate dose-response model and the interpretation of highly imperfect epidemiological studies make it impossible to develop unit risk estimates for any of the three substances that can be defended rigorously. The unit risk estimates used in Part II, however, probably reflect an upward bias, primarily because they were derived solely from the linear model.¹⁸¹

To the extent that the unit risk factors are too high, the expected benefits of controls are overestimated. Revising those estimates downward reinforces the earlier conclusions that benzene and acrylonitrile controls are not cost-effective. 182 It also reinforces the conclusion that uniform BAT standards on all three sources of emissions from coke oven plants would not be cost-effective relative to less stringent regulations, 183

D. Uncertainties in Valuing Risk Reduction

Critics of the use of benefit-cost analysis to evaluate environmental policy often focus on the difficulty of assigning a "value to life." The empirical studies of wage premiums for occupational risk cited in Part II cover a wide range, from several hundred thousand to several million dollars per life saved. Even that wide range, however, is sufficient to reject BAT standards for maleic anhydride plants and for all four types of plants emitting acrylonitrile. It is also sufficient to indicate cost-beneficial modifications of the coke oven regulations, though not sufficiently precise to determine if more limited regulation of coke ovens is justified.

Several objections can be raised to the use of wage premium studies to value risks reduced through environmental regulation. If workers are not fully aware of the risks they run, wage premiums will not reflect the workers true willingness to accept risk in exchange for higher pay. 185 In addition, dangerous jobs tend to be filled by individuals willing to accept risks for lower compensation. 186 Thus, even if the wage premium studies accurately measure trade-offs acceptable to workers studied, they may underestimate the general population's willingness to pay for reduced risk.

Despite these criticisms, some simple examples suggest that the higher end of the range of values estimated by the wage premium studies is more likely an overestimate than an underestimate. If the value per life saved is \$5 million, for example, the government should impose auto safety regulations that cut the risk of traffic fatalities in half as long as the control cost per new car is less than \$12,500.187 With that same value

^{175.} See Address by S. Lamm to the EPA in Washington, D.C. (Aug. 21, 1980) (testimony for the American Petroleum Institute at hearings on the proposed standard for maleic anhydride plants) [hereinafter cited as Address by Lamm]; see also R. Luken & C. Miller, Regulating Benzene: A Case Study (Sept. 1979) (U.S. EPA unpublished paper).

^{176.} See supra notes 80-89 and accompanying text (discussing the cost-effectiveness of benzene).

^{177.} See Final EPA Benzene Assessment, supra note 65. Studies included: one of workers in two plants using benzene as a solvent to make a transparent film, see Infante, supra note 81, at 76-78; another of Turkish shoe workers using benzene-based adhesives, see Aksoy, Leukemia in Shoe Workers Exposed Chronically to Benzene, 44 BLOOD 837 (1974); Aksoy, Types of Leukemia in Chronic Benzene Poisoning: A Study in Thirty-Four Patients, 55 ACTA HAEMATOLOGICA 65 (1976); Aksoy, testimony before Occupational Safety and Health Administration, Washington, D.C. (July 13, 1977); and the third of workers in chemical plants using benzene, see Ott, Townsend, Fishbeck & Langner, Mortality Among Individuals Occupationally Exposed to Benzene (Exhibit 154) (OSHA Benzene Hearings July 19-Aug. 10, 1977).

^{178.} Critics have raised issues including the CAG's exposure estimates for all three studies, its inclusion of the deaths of two workers not in the original cohort of the Infante study, its failure to exclude workers exposed to other hazardous chemicals in the Ott study, and its estimate of the baseline risk in the Aksoy study. See Nichols, supra note 42, at 170 (summarizing the criticisms of the CAG study); Address by Lamm, supra note 175.

^{179.} See R. Luken & C. Miller, supra note 175.

^{180.} Address by Lamm, supra note 175, at 4.

^{181.} See supra notes 170-75 and accompanying text. For benzene, several studies suggest further that the CAG has overestimated the linear model's coefficient. See supra notes 176-80 and accompanying text.

^{182.} See supra notes 117-24 and accompanying text, See also supra notes 132-140 and accompanying text.

^{183.} See supra notes 125-31 and accompanying text.

^{184.} See, e.g., Doniger, supra note 23. at 518-19; Rodgers, Benefits, Costs, and Risks: Oversight of Health and Environmental Decisionmaking, 4 HARV. ENVIL. L. REV. 191, 196-98 (1980).

^{185.} See Raiffa, Schwartz & Weinstein, Evaluating Health Effects of Societal Decisions and Programs, in Decision Making in the Environmental Protection Agency (1977).

^{186.} Id. at 37.

^{187.} As there are roughly 50,000 automobile-related fatalities each year, such a :echnology would save 25,000 lives annually. If the value per life saved is \$5 million, then the value of the technology would be \$125 billion. If we assume further that there are 10 million new cars sold each year, then the technology would be worth up to \$12,500 per car. See Haigh, Harrison & Nichols, supra note 12, at 68.

per life saved, a family of four with the median yearly income should be willing to give up about one half of that income in order to face the average overall death rates that prevailed in 1975 rather than those from 1970.188

A more fundamental philosophical objection is based on the distinction between voluntary and involuntary risks. ¹⁸⁹ Individuals are free to choose their jobs (and their cars). In contrast, people, as individuals, have little choice about the quality of the air that they breathe. Society should be willing to pay much more to avoid such involuntary risks, the argument continues, than individuals would spend to reduce hazards over which they have personal control. Supporters of benefit-cost analysis reply that it makes little sense for the government to make fundamentally different trade-offs than individuals would when confronted with similar private choices. ¹⁹⁰ Decisionmakers, however, may be especially concerned about distributional implications if the risks are unusually large and concentrated among a small group of individuals. ¹⁹¹

Two factors suggest that, in general, a lower value should be ascribed to lives saved through the regulation of environmental carcinogens than to many other public choices involving risk. First, cancer is disproportionately a disease of the elderly, so each life "saved" represents relatively few additional years of life. 192 Regulatory programs should be evaluated in terms of years of life saved, not total lives saved. 193 This suggests that the value per life saved should be lower for evaluating regulations to control carcinogens than for analyzing other programs, such as highway safety, that prevent the deaths of younger people.

The second factor is the substantial delay between control expenditures and reductions in risk due to time lags between exposure to carcinogens and the onset of disease. Conventional benefit-cost analyses discount streams of benefits and costs to reflect the time value of money. Economists differ as to whether discounting should be applied to health

benefits. 194 Most theoretical discussions support discounting, 195 but in common practice the timing issue is ignored. 196

Discounting reduces the relative value of saving lives through control of environmental carcinogens, because the benefits of reducing exposure are realized many years after the costs are incurred. At a discount rate of five percent, for example, a twenty-year time lag reduces the value of risk reduction by sixty-two percent compared to an immediate risk reduction, say through improved fire protection. 197

The valuation of risk reduction remains uncertain and highly contentious, with little prospect for agreement on any particular dollar value for saving a life. The problem is at least as much one of ethics and politics as it is one of science and the interpretation of empirical evidence. EPA, however, cannot avoid making trade-offs between protection and control costs, whether it does so explicitly or implicitly. Fortunately, precision may not be very important because many decisions are correct over wide ranges of values. Moreover, it is possible to narrow the range presented earlier by reducing the high end. Values much in excess of \$1 million per life saved appear difficult to justify, particularly for airborne carcinogens for which the benefits are delayed and the lives saved are relatively short.

E. Unquantified Benefits 198

EPA's procedures almost certainly overstate the cancer-reduction benefits of controlling hazardous air pollutants. By focusing solely on cancer in its quantitative estimates for section 112 pollutants, however, the EPA may miss other important health and environmental benefits.

Many carcinogens, including the three considered here, have also been associated with non-cancer health effects at relatively high doses. 199 For most of these non-cancer effects, however, scientists generally accept

^{188.} See Bailey, supra note 70, at 45-46,

^{189.} See E. CROUCH AND R. WILSON, supra note 165, at 85.

^{190.} See, e.g., Zeckhauser, supra note 67, at 419.

^{191.} For a general discussion on distributional effects of environmental regulations, see Harrison, supra note 163; Harrison and Portney, Who Loses from Reform of Environmental Regulation in Reform of Environmental Regulation (W. Magat ed. 1982). See also D. HARRISON, WHO PAYS FOR CLEAN AIR? (1975) (discussing the cost and benefit distribution of federal automobile emission standards).

^{192.} The death rate for the type of leukemia associated with benzene, for example, is more than 26 times higher among people aged 70 to 74 than among children aged 1 to 5. See Final EPA Benzene Assessment, supra note 65, at Table 1.

^{193.} Zeckhauser and Shepard argue that mortality benefits should be summarized in terms of the discounted number of "Quality Adjusted Life Years" (QALYs) saved. Their QALY measure adjusts benefits to include reductions in the quality of life due to disability, for example. See Zeckhauser & Shepard, Where Now for Saving Lives?, 40 LAW AND CONTEMPORARY PROBS, 5 (Autumn 1976).

^{194.} See, e.g., Raiffa, Schwartz & Weinstein, supra note 185, at 42-49.

^{195.} See, e.g., id. at 49.

^{196.} See, e.g., Page, Harris & Bruser, Removal of Carcinogens from Drinking Water: A Cost-Benefit Analysis (Jan. 1979) (Social Science Working Paper #230, California Institute of Technology, Pasadena, Cal.).

^{197.} The equation for discounting is $B/(1+r)^x = PV$, where B is the benefit in current dollars, r is the discount rate, x is the number of years from today in which the benefit accrues, and PV is the present value of the benefit. In the example given, r equals .05 and x equals 20; the present value of the benefit today (PV) is 37% of B.

^{198.} This article, and therefore this section, considers only human health benefits; no consideration is given to benefits related to reduced wildlife and plant damage from these toxic substances. See, e.g., Acrylonitrile Assessment Document, supra note 77, at 88-100 (describing the effects of acrylonitrile on plants, domestic wildlife and aquatic organisms).

^{199.} Office of Research & Dev., U.S. Envtl. Protection Agency, Assessment of Health Effects of Benzene Germane to Low-level Exposure 48-65 (1978) (EPA-600/1-78-061) (noting benzene's association with aplastic anemia and other serious blood disorders)

the concept of zero-risk thresholds, and current environmental exposures appear to lie far below the relevant levels.²⁰⁰

Chromosomal damage — mutagenic effects — may be an exception, as scientists are less willing to assume that such effects have thresholds.²⁰¹ All three of the case study pollutants appear to cause chromosomal damage.²⁰² None, however, has been associated with birth defects, and analyses by EPA's health experts emphasize mutagenic evidence as corroborating the carcinogenicity of the substance, rather than as a separate concern.²⁰³

The "conventional pollutant" benefits associated with controlling some hazardous air pollutants may be more significant. States have regulated benzene and acrylonitrile to help meet the ambient standard for ozone. ²⁰⁴ Coke ovens have been regulated to meet the particulate ambient standard. ²⁰⁵ In addition, controls on section 112 pollutants may also control other pollutants. If maleic anhydride plants use incineration to control benzene emissions, for example, they would also reduce carbon monoxide, a "conventional" pollutant covered by an ambient standard. ²⁰⁶

Occupational exposure represents still another potentially important omitted benefit category. Some controls designed to reduce emissions to the ambient environment also reduce the exposure of workers. This effect is most likely to be significant when the emissions are from low-level, fugitive sources, as is true of coke ovens. If the sources are elevated stacks, as with maleic anhydride plants emitting benzene and the acrylonitrile plants, environmental controls are unlikely to have much impact on workers.

The importance of these omitted benefit categories varies widely across specific regulations. In the three cases discussed, they do not affect the basic conclusions for maleic anhydride plants and acrylonitrile, primarily because the cancer benefits are so small in those cases and the

[hereinaster cited as Health Effects of Benzene]; EPA Coke Oven Assessment, supra note 90, at 54-63 (noting the acute and chronic toxicity of coke oven emissions); Acrylonitrile Assessment Document, supra note 77, at 116-48 (noting the acute, subacute and chronic toxicity of acrylonitrile).

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only potentially important omitted benefits appear to be those associated with conventional pollutants. To the extent that such benefits are important, benzene and acrylonitrile are probably best addressed by the framework established for other conventional pollutants — state implementation plans for existing sources and new source performance standards for new ones.

The omitted benefit categories are more troubling for the coke over case, primarily because it is a closer decision on the basis of cancer reduction benefits alone. The quantitative significance of the additional benefits from reduced worker exposure and reduced particulate emissions cannot be evaluated, but it seems unlikely that they would be sufficient to justify the uniform BAT standard over the alternatives of a less stringent uniform standard or a differential stategy targeted at high exposure plants.

F. Summary

Huge uncertainties pervade estimates of the benefits of regularing airborne carcinogens. As a result, the figures presented in Part II must be viewed with a strong dose of skepticism; they may well be in error by orders of magnitude. These uncertainties, however, do not alter the major conclusions of the case studies.

The clearest conclusions emerge for the four source categories emitting acrylonitrile. The cost-effectiveness ratios for emission controls were ten or more times higher than the plausible range of values for risk reduction. ²⁰⁷ Nothing in this section has suggested that benefit estimates err by that margin. ²⁰⁸

The calculations for benzene emitted from maleic anhydride plants gave a substantially narrower result, although the estimated cost per life saved was still in excess of \$6 million.²⁰⁹ Several factors suggest that an accurate estimate of the expected cost-effectiveness ratio would be substantially higher. They include: (1)-the general issue of the appropriate dose-response model;²¹⁰ (2) evidence that the CAG overestimated the linear model's risk factor;²¹¹ and (3) a significant rise in the cost per life saved when the estimates are adjusted for less than full capacity operation.²¹²

The most ambiguous results arise in the case of coke ovens, although a BAT standard for charging emissions almost certainly would fail a

^{200.} See, e.g., Nichols, supra note 42, at 152 (benzene).

^{201.} Id. at 162.

^{202.} See Acrylonitrile Assessment Document, supra note 77, at 156-66; Final EPA Benzene Assessment, supra note 65, at app. 1-5; EPA Coke Oven Assessment, supra note 90, at 27-52.

^{203.} See, e.g., Final EPA Benzene Assessment, supra note 65, at app. 1-5.

^{204.} See, e.g., [3 State Air Laws] ENV'T REP. (BNA) 521:0621, 521:0631-:0664 (1983) (Texas' regulation of volatile organic compound emissions); [1 State Air Laws] ENV'T REP. (BNA) 346:0501, 346:0521 (1983) (Florida's regulation of volatile organic compound emissions).

^{205.} See, e.g., [1 State Air Laws] Env't Rep. (BNA) 301:0501, 301:0513-:0515 (1982) (Alabama's restrictions on coke oven emissions); id. at 336:0501, 336:0512 (1984) (Delaware's restrictions on coke oven emissions); [2 State Air Laws] Env't Rep. (BNA) 411:0501, 411:0516 (1982) (Michigan's restrictions on coke oven emissions).

^{7 &#}x27;5 Fed. Reg. 26,660, 26,661 (1980).

^{207.} See supra notes 132-140 and accompanying text.

^{208.} Unless, of course, one favors a nonlinear dose-response model, but that would cut in the other direction.

^{209.} See supra notes 87-89 and accompanying text.

^{210.} See supra notes 167-175 and accompanying text.

^{211.} See supra notes 176-180 and accompanying text.

^{212.} See supra notes 145-146 and accompanying text.

benefit-cost test.²¹³ Whether the uniform door and topside standards generate positive expected net benefits remains in doubt. Two issues raised in Part III, however, weigh against those standards: (1) the likelihood that the pure linear model overestimates the expected risk;²¹⁴ and (2) the evidence suggesting that a value on risk reduction much in excess of \$1 million per life saved cannot be justified.²¹⁵ In fact, it is unclear whether even differential standards limited to high-exposure coke plants would yield positive net benefits. Such standards, however, unquestionably represent an alternative superior to uniform BAT standards.

G. Postscript

Recent developments reinforce our conclusions regarding benzene emitted from maleic anhydride plants and cast further doubt on the wisdom of imposing standards on coke ovens. After the maleic anhydride standard was proposed in 1980, five important changes took place: (1) four plants shut down; (2) two plants converted to n-butane, apparently in response to higher benzene prices; (3) the largest plant installed controls and began to convert all of its capacity to n-butane; (4) an additional plant was "discovered;" and (5) EPA reduced the BAT standard to the equivalent of ninety percent control. 216 As a result, had the standard been imposed, it would have applied only to the newly discovered plant, a small one located in a lightly populated area, and the estimated health gain would have been to prevent approximately one case of cancer every 300 years. 217 Citing those minimal potential health impacts, the EPA withdrew the proposed standard for maleic anhydride plants in early 1984. 218

More recent estimates from the EPA indicate that coke oven plants also pose a smaller threat than estimated earlier. Data in a recent EPA report suggest that the BAT standards would save less than five lives per year, in contrast to over ten lives per year estimated on the basis of the earlier data. The newer EPA estimates rely on higher emissions but much lower exposures, based on newer modeling using meteorological data for each plant.²¹⁹ Even more recently, the CAG lowered its estimate of unit

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risk and the EPA learned that additional plants have shut down, so the estimated annual reduction in cancer cases has fallen to about two. 220 It thus appears that coke ovens are no longer a "close" case; although no cost estimates are available for the closed plants, the estimated cost per case avoided for the BAT standards must be well in excess of \$5 million.

IV. FINDINGS

The three case studies illustrate many of the problems and uncertainties involved in estimating the benefits of environmental regulation. Although benefit-cost analyses of such regulations can never be very precise, these studies suggest that quantitative assessments of benefits can provide valuable information to regulators interested in improving the efficient use of society's resources. In this Part, some of the lessons from the case studies are summarized, first with respect to section 112 of the Clean Air Act and then with respect to the more general use of benefit-cost analysis to evaluate strategies for regulating health-threatening pollutants.

A. Section 112

In dealing with "hazardous air pollutants" covered by section 112 of the Clean Air Act, the EPA has consistently followed a technology-based approach to regulation. The "generic" policy proposed in 1979 would have formalized this approach in an attempt to speed up and routinize the process of listing and regulating such substances. ²²¹ More recently, some members of Congress have suggested forcing EPA regulation of section, 112 pollutants by giving the agency a deadline for making decisions on a list of thirty-seven substances. ²²² The BAT approach to regulation is flawed because it implicitly treats airborne carcinogens as a homogeneous class. The case studies indicate that airborne carcinogens are a very heterogeneous class, with wide variations in benefits (and costs) across substances and source categories.

1. Heterogeneity

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Even within a small sample of three pollutants studied, the risk reduction benefits from controlling emissions vary enormously because of differences in carcinogenic potencies and in exposure patterns. Each kilogram of coke oven emissions, for example, causes about 500 times as much cancer risk as a kilogram of acrylonitrile or a kilogram of benzene emitted from a maleic anhydride plant.²⁷³ Regulatory analyses that focus

^{213.} See supra notes 125-127 and accompanying text.

^{214.} See supra notes 167-175 and accompanying text.

^{215.} See supra notes 67-72 and accompanying text.

^{216.} See A. NICHOLS, TARGETING ECONOMIC INCENTIVES FOR ENVIRONMENTAL PROTECTION 157 (1984).

^{217.} Id.

^{218, 49} Fed. Reg. 8386 (1984).

^{219.} See Office of Air Quality Planning & Standards, U.S. Envtl. Protection Agency, Coke Oven Emissions from Wet-Coal Charged By-Product Coke Oven Batteries — Background Information for Proposed Standards (Sept. 1983) (draft EIS) (Research Triangle Park, N.C.). This document does not calculate reductions in stalities or exposure. It does, however, include estimates of unit risk and baseline emissions and cancer cases, from which it is possible to measure average exposure per unit of emissions. The document also gives estimates of emission reductions, from which reductions in cancer cases can be estimated.

^{220.} Personal communication from Teresa Gorman, Office of Policy, Planning & Evaluation, U.S. Envtl. Protection Agency, Washington, D.C. (Apr. 12, 1984).

^{221.} See supra notes 43-50 and accompanying text.

^{222.} See supra text accompanying notes 55-56.

^{223.} See Haigh, Harrison & Nichols, supra note 12, at Table 2.1.

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on the feasibility and affordability of controls ignore these critical differences.

The cost per unit of risk reduction also varies greatly across the three cases, differing by a factor of more than 100 between coke plants and the least cost-effective acrylonitrile category. These wide variations suggest that a policy of applying BAT standards to all sources emitting airborne carcinogens imposes higher than necessary costs to achieve any given level of overall risk reduction. Individual substances and source categories must be considered on their own merits, taking account of potencies and exposure levels as well as technology and affordability.

2. Modest Benefits From Control

The desirability of strict regulations on airborne carcinogens is easily overstated. In both the benzene and the acrylonitrile cases, for example, a small number of sources emit millions of kilograms of proven human carcinogens each year. Moreover, the controls being considered are eminently affordable; their costs are estimated at less than two percent of total sales.224

The case studies show, however, that only modest health benefits are likely to result from the regulations. BAT standards for both acrylonitrile and maleic anhydride plants would have a combined effect of avoiding less than one cancer death per year. The coke oven standards would provide substantially larger benefits, but even in that case the gain in public health seems rather modest for standards that apply to a major industry on a nation-wide basis.

Of course, it is not certain that all section 112 regulations would yield similarly small benefits. The case studies, however, cast doubt on the proposition that control of airborne carcinogens will lead to major reductions in the nation's cancer burden. The fact that the pollutants considered here have been assigned relatively high priority by EPA reinforces this skepticism.

B. The Role of Benefit-Cost Analysis

1. Evaluating Proposed Regulations

Existing methods of quantitative assessment may not yield clear answers as to the cost-effectiveness of regulations in all, or even most, cases. Many of the components in benefit estimation are highly uncertain. Because the final estimate typically is a multiplicative function of these individual components, the overall level of uncertainty is extremely high. Nonetheless, robust conclusions often can be drawn to help regulators avoid imposing some regulations for which the benefits are far smaller than the costs. Benefit-cost analyses may also identify regulations that clearly provide positive net benefits, although none of the instant case studies identified such a regulation.

224. See, e.g., supra text accompanying notes 87-88.

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2. Improving Regulations

Most discussion of benefit-cost analysis focuses on its role as a "test" for proposed regulations. Benefit-cost analysis is even more useful, however, as a tool for designing regulations. In all three of the case studies. less stringent controls yielded most of the benefits of the BAT standards at far lower cost. Although none of these modified uniform standards resulted in clearly positive net benefits, all were more efficient than the original BAT standards. If benefit-cost principles were applied early in the regulatory process and used to guide the selection of control options for detailed analysis, even larger gains could be realized.

The case studies indicate that regulatory efficiency is maximized by exploiting marginal differences in the benefits of control among sources. These differences arise primarily because of differences in population densities around plants: the public health benefits of controlling emissions are far larger in cities than in lightly populated rural areas. In all three cases, restricting standards to areas where the marginal benefits of control are relatively high led to impressive efficiency gains over uniform. standards.

3. Information Requirements and Delays

If they are to be useful to decisionmakers, analytic techniques can not rely on data that are unduly expensive or time consuming to obtain. Analysis is not free; it consumes scarce resources that could be put to other uses and may cause delays in an already lengthy regulatory process. Fortunately, a great deal can be done with information that is already collected by EPA. Also, a sharper set of decision criteria should speed up rather than delay the regulatory process. Note that the technical data for all three case studies were based on information developed as part of EPA's BAT strategy for controlling hazardous air pollutants. Thus, performing the kinds of analyses presented in this article should not significantly increase either the costs or the delays of the regulatory process.

For relatively close decisions, such as the coke oven case, additional information could prove useful, particularly in four areas: (1) cost and emissions estimates for a wider range of control options; (2) more plantspecific data for exposure estimates (as were recently developed by EPA for coke ovens); (3) estimates of non-cancer benefits, particularly those associated with conventional pollutants (such as ozone and particulate matter); and (4) development of techniques for estimating the expected level of cancer as well as the "plausible upper bound" now used by EPA.

Adoption of benefit-cost principles could reduce the amount of information required to regulate in many cases. Current efforts, for example, typically include studies of the "economic impact" of regulations, attempting to predict their effects on plant closings, product prices, and the like. Such impacts are of second-order importance relative to the direct benefits and costs of control. Application of benefit-cost principles in allocating agency resources may also reduce the costs of analysis by leading to the curtailment of the regulatory process before large expenses

have been incurred to gather data. The acrylonitrile case provides an excellent example; some crude analysis early in the regulatory process—based on the unit risk factor, existing levels of control, and average exposure factors—probably would have indicated the minimal potential benefits involved and consequently eliminated the need for detailed analysis of control technologies and costs.

C. Conclusion

Pleas for the use of benefit-cost analysis in environmental decisionmaking are commonplace. This article contributes to the discussion by illustrating how benefit-cost techniques might be employed to evaluate individual regulations, to identify promising alternatives, and to evaluate the robustness of regulatory choices relative to uncertainties. Although the case studies reviewed here assess particular regulations for airborne hazards, the conclusions regarding the usefulness of benefit-cost principles apply more generally.

Over two dozen federal statutes require the regulation of toxic or hazardous substances.²²⁵ Some of these explicitly call for a balancing of benefits and costs,²²⁶ while others use a "reasonableness" standard that would permit such an analysis.²²⁷ Those statutes that explicitly permit the consideration of only health effects tend to deal with food products or common consumer items.²²⁸ Thus, a benefit-cost analyis, although not applicable to all situations, could be applied far beyond the Clean Air Act.

The advantages of benefit-cost principles must, however, be put into perspective. A benefit-cost analysis of an environmental program is not a substitute for good science or good judgment. To the contrary, explicit estimation of health risks, and the amount that controls will reduce those risks, provides a context for incorporating both science and judgment into regulatory decisions. Cruder rules based solely upon evidence of carcinogenicity or technological feasibility of control hide the real choices involved in regulating health-threatening substances.

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^{225.} Office of Toxics, U.S. Envtl. Protection Agency, Chemical Substances Designation (Dec. 1981).

^{226.} See, e.g., Environmental Pesticide Control Act, 7 U.S.C. §§ 136b(b), 136a(c)(5) (1982); Federal Hazardous Substances Act, 15 U.S.C. § 1262(i) (1982); Toxic Substances Control Act, id. § 2605(c) (1982); Food, Drug & Cosmetics Act, 21 U.S.C. § 346a(b)(1) (1982); Atomic Energy Act, 42 U.S.C. §§ 2022(a), 2022(b), 2114(a) (Supp. V 1981).

^{227.} See, e.g., Poison Prevention Packaging Act, 15 U.S.C. § 1472(b) (1982); Hazardous Liquid Pipeline Safety Act, 49 U.S.C.A. § 2002(b) (West Supp. 1983).

^{223.} See, e.g., Food, Drug & Cosmetics Act 21 U.S.C. §§ 342(a)(2)(A), 348(c)(3)(A), 360(d)(1)(H), 376(b)(5)(B), 451, 601, 1031 (1982); Lead Based Paint Act, 42 U.S.C. § 4831 (1976 & Supp. V 1981). Other non-consumer statutes also focus exclusively on health factors. See, e.g., Surface Mining Control and Reclamation Act, 30 U.S.C. §§ 1265(b), 1266(b)(9)(A) (Supp. V 1981), Marine Protection, Research, and Sanctuaries Act of 1972, 33 U.S.C. § 1412(a) (1976).

Friday, September 6

| | Regulatory Aspects | |
|----------------|---|------------------|
| 8:30 - 9:30 | Legislative & Regulatory Aspects of Risk | Brown |
| 9:30 - 9:45 | Refreshment Break | |
| <u>Risk Ar</u> | <u>Discussion Session -</u> nalysis for Specific Contaminants | |
| 9:45 - 11:15 | 1. ALAR (Daminozide) | Graham |
| 11:15 - 12:30 | 2. Dioxin | Birnbaum |
| 12:30 - 1:15 | Lunch | |
| 1:15 - 2:00 | 3. Lead | Hu |
| 2:00 - 2:30 | General Discussion | Staff |
| 2:30 - 2:45 | Refreshment Break | |
| | Course Closing | |
| 2:45 - 3:30 | Risk in Perspective | Wilson |
| 3:30 - 3:45 | Course Critique & Evaluation | Moeller & Wilson |

Legislative & Regulatory Aspects of Risk

Brown

Legislative and Regulatory Aspects of Risk

David R Brown ScD.

I. Introduction:

The application of risk assessment at the state level a unique problem due to the pressure for rapid timely decisions, immediacy of political factors and the roles of state agencies. This hour will explore risk assessment at the state level as it is currently conducted in a New England state, Connecticut.

First the state regulatory situation will be described showing that the risk assessment process follows the guidelines set forth in the federal programs. Perspective is provided as an overview of the process. This will be followed by discussion of three risk assessment problems currently under discussion, dioxin in air standard, drinking water standards and radon in water standards.

III. Perspective

- A. Separation of management from risk assessment.
- B. Unique role of Departments of Health.
 - 1. Regulatory powers.
 - 2. Interstate communication.
- C. A differing view of uncertainty.
- $-\,$ D. Myth of regulation,the Role of Good Science
 - 1. It is believed that regulatory standards rest or should rest on on a scientific base. Thus if the regulations are good they must rest on good science. It follows from the above that effort needs to be expended to assure that regulations are scientifically defensible and credible to sustain pollution control decisions. (Paraphrased from former head of SAB)
 - 2. There are several myths around regulations and the regulatory process. This is shown by the interaction of science with politics as it relates to three questions derived from the above and show that the level of misunderstanding is unacceptably high.

3. Key questions about the process;

- ≈a. Is bad science responsible for bad regulation?
- b. Would improved precision in science improve regulation?
- -c. Have review boards improved the process from a public health perspective?

To reveal my bias at the outset I would answer NO to all of the above.

III. Background

- A. Characteristics of "good science"
 - 1. Controlled studies
 - 2. Valid methods
 - 3. Identification of test substances
 - 4. Verification of conclusions

→B. Characteristics of good regulation

- 1. Complete analysis of the data
- 2. Determination of limitations
- 3. Plausibility of the conclusions
- 4. Timely decisions
- C. Nature of the problem
 - 1. Items number 4 in A and B above are in conflict
 - 2. Not to decide is to decide
 - Public health is not compatible with exposures while waiting to decide, eg ALAR, ASBESTOS, RADON
- D. perceived conflicts in rights
 - 1. Individual vs corporate rights
 - 2. Articles IV and V of the Constitution
 - 3. Economic realities
- E. Examples of interactions of science and policy
- Poor science and good policy
 Chloridane
- 2. Poor science and poor policy

Asbestos Alar 3. Good science and poor policy

> Ethylene dibromide Benzene

4. Good science and good policy

Methylene chloride Most OP pesticides Radon

- F. Illustration of the need for risk assessment.
 - 1. The typical environmental exposures.
 - 2. The typical research protocol
 - 3. Application of data to reduce uncertainty
- IV A state's approach to ground water contamination.

The assessment and mitigation of groundwater contamination which affects private drinking water is one of the most difficult problems facing the health and environmental agencies at the state and local levels.

A primary aspect of the problem is the need to make an immediate decision to terminate potential exposures even though the contaminants, their actions and the levels of exposures are not known. It is also important to acknowledge that water is essential for habitability of the home.

This leaves the health official with need to make a decision with less than complete information. As a matter of principle these decisions should be health based and must be protective of public health. The decisions should also be defensible in the scientific sense.

There is a fundamental difference in the goals of academic research and the need to reach a policy position. An academic researcher who is faced with

incomplete data correctly refuses to decide but waits for more data but this is a decision a public health official needs to decide because to wait is a decision in it self.

The decision needs to have the following characteristics it must be protective of the public health it must be timely, it should be accurate and it should comply with the regulations.

If there is no regulation the basis for these decisions is the general powers of the commissioner to protect the public health. This was not working in connecticut so the state set up a procedure for handling the situations

It is important to also understand the scope of the problem. Over the last ten years Connecticut has had over 1400 wells contaminated. These wells served 300,000 people. Under these circumstances it is not possible to Handle individual instances with a risk assessment approach.

A joint program has ben developed between the departments of health services and the Departments of environmental protection. Within Health Services the process involves two groups the toxic hazards section which is responsible for risk assessment and the water supplies section which is responsible for correcting the problem.

The process is based on a statute within the Dept of environmental protection. The bottled water law.

- V. The state Dioxin standard
 - A. Criteria for standard
 - B. Legislatures role.
- VI. The water radon standard
 - A. Background radon data
 - B. Effect of the strict standard setting process
- VII. Summary.

Risk Analysis (Accepted) Dec. 1990

CONNECTICUT'S DIOXIN AMBIENT AIR QUALITY STANDARD

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ABSTRACT

.ಕರಿ ಕ್ಷಮತ ಎಂದು ಕಿಳಿ ಈ ಅಂಗಳ Connecticut is the first state in the country to have adopted an ambient air quality standard for dioxins at 1 pg/m^3 , 2,3,7,8-TCDD equivalents, as annual average. This paper describes the scientific basis and the methodology used by the State Department of Health Services (the risk assessment agency) in assisting the Department of Environmental Protection (the risk management agency) to establish a health-based dioxin standard. This standard protects the public health from the aggregate effect of all sources of dioxin emissions in the vapor and particulate phases. The risk assessment methodology included: a limit on total daily dioxin exposure from all media and sources based on reproductive effects, a multi-media non-source specific exposure assessment, an apportionment by media of the health-based limit (including background dosing rate), an evaluation of inhalation bioavailability and cancer risk based on a calculation of a range of upperbound cancer risk estimates using different potency, bioavailability, and particle phase assumptions.

.' <u>Key Words</u>. Reproductive Effects, Multi-media Exposure, Dose Apportionment, Bioavailability, Carcinogenic Potency.

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INTRODUCTION

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This report describes the scientific basis for Connecticut's primary Ambient Air Quality Standard (AAQS) for dioxins established by the State Department of Environmental Protection (DEP) at 1 picogram per cubic meter (1 pg/m³) 2,3,7,8-TCDD equivalents as annual average (a picogram is one trillionth of a gram). Dioxins and 2,3,7,8-TCDD are used interchangeably in this report. The dioxin AAQS is based on the State Department of Health Services' (DHS) analysis of a Dioxin Health Risk Assessment prepared by Hart Associates. (1) The Health Risk Assessment was prepared in response to a legislative mandate, and designed to be consistent with DEP's Air Toxics Program requirements. (2) Thus, the standard setting process was a bilateral effort, which utilized the expertise of the DHS in risk assessment, and of the DEP in risk management. A Scientific Panel served as an advisory body.

The details of the Dioxin Risk Analysis, the key assumptions used, and their rationale are presented below:

DIOXIN DAILY DOSE AND BODY BURDEN

The risk analysis developed a rationale for consideration of daily dose and body burden for dioxins which are independent of specific sources. This was considered appropriate for the following reasons:

First, dioxin exposure is multimedia in nature. Dioxins have been detected in air, soil, sediments, suspended sediments, water, fish, meat, and milk as well as in human adipose tissue, breast milk, and blood.(3,4) The total body burden represents the sum of potentially significant individual contributions from the various media, sources and routes of human exposure. By comparing the relative contributions from each medium with the health-based limit, significant exposures can be identified and necessary measures taken to reduce such exposures.

Second, the evidence suggests that there exists a background body burden of dioxins in the general population of industrialized nations. (3) The body burden measurements provide an indication of past exposure, and can be used to calculate the total daily dioxin intake from the background exposure. The health impact from this daily background exposure can be assessed, and thus incorporated into the standard setting process. However, the ways in which all of the various media, sources and routes contribute to this background exposure remain unknown. Although there are uncertainties in assessing exposures, an advantage of this approach is that it places the various media of exposure, including the overall background multi-media exposure, in perspective.

REPRODUCTIVE EFFECTS AND DOSE LIMIT

Reproductive, developmental, and carcinogenic effects were determined to be health impacts of concern and were evaluated. Animal studies on 2,3,7,8,-TCDD toxicity have clearly demonstrated that it is a developmental and reproductive toxin in a variety of species at relatively low doses. A review of the pertinent developmental and reproductive studies can be found in EPA's Health Assessment Document for PCDDs. (5) The reported adverse outcomes include reduced fertility, litter size and survival, offspring body weight changes, as well as cleft palate and kidney abnormalities. Among the available studies, Murray et al's (6) 1979 study on Sprague Dawley rats, and Allen et al's (7) 1979 study on rhesus monkeys were considered appropriate for quantitative assessment.

Murray et al's study examined the effects of dietary exposure to 2,3,7,8-TCDD on reproduction in Sprague Dawley rats over three generations. The rats were given 0, 0.001, 0.01, and 0.1 ug/kg/day. No significant toxic effects were observed in the F_0 generation during 90 days treatment prior to mating. The study showed that the lowest dose, 0.001 ug/kg/day had no effect on fertility, litter size or fetal survival. The authors concluded that the doses 0.01 and 0.1 ug/kg/day produced significant effects on the reproductive capacity through three generations, F_0 , F_1 , and F_2 . The study indicated that the 0.001 ug/kg/day could be considered as a no effect level. A reanalysis of the Murray et al data using a different statistical approach concluded the lowest dose was an effect level and that a no effect level could not be determined. (8) Since there was a question relative to the no effect level in the rat study, DHS considered the data on 2,3,7,8-TCDD's effects on reproduction in rhesus monkeys. The doses administered in

the diet were 0, 1.8 (50 ppt) and 18 ng/kg/day (500 ppt) up to 9 months. Following 7 months of treatment, the females were mated with untreated males. At the higher dose (18 ng/kg/day), there was a decrease in serum estradiol and progesterone. The menstrual cycle was however not affected. Only three animals conceived, after which two aborted and one had a normal birth. At the 1.8 ng/kg/day dose serum estradiol and progesterone levels were normal. Eight treated females were mated with untreated males; there were six pregnancies, four abortions and two normal births. DHS judged that the results of the sensitive rhesus monkey studies could potentially support a more conservative effect level than that reported in the rat studies. Accordingly, the 1.8 ng/kg/day lowest effects level was used to calculate a health-based limit on the total dioxin daily intake from multimedia exposure.

Besides reproductive effects, tumorogenic effects have been observed in rodent experiments following chronic exposure to low levels of 2,3,7,8-TCDD. For example, Kociba et al's 1978 two year study tested cancer response in rats at doses of 1, 10, and 100 ng/kg/day. The 10 ng/kg/day dose caused a statistically significant increase in liver tumors in experimental animals versus controls. (9)

A comparison of the rodent dose-response data from the cancer study by Kociba (9) and reproductive study by Murray (6) showed that the two experimental adverse outcomes observed in separate bioassays, reduced fertility and liver tumors, appear to be the result of exposure to equi-toxic doses of 2,3,7,8-TCDD, i.e., 10 ng/kg/day. The experimental exposure durations were different, 3 months for first reproductive effects, and 24 months for tumor effects (time to fatal tumor data are not available). For a congener like 2,3,7,8-TCDD, the cumulative dose is more critical than the dose rate. (10) The data from reproductive and cancer bloassays support this view. By factoring the exposure duration and calculating the cumulative dose for each outcome, it can be shown that 12 to 25 percent of the cumulative cancer dose causes fertility effects in the same species. The cumulative dose analysis suggests that the potential adverse reproductive effects from dioxin exposure present a substantial immediate concern and cancer is a chronic concern at the same levels of exposure. The data from the rhesus monkey studies by Allen et al (7) provide further support to the argument that the reproductive response is a very sensitive response. The experimental evidence points to a lower Lowest Observed Effect Level (LOEL), 1.8 ng/kg/day, compared with a LOEL of 10 ng/kg/day, identified in the rat studies. Factoring these values, and the exposure duration of six months in the non-human primate studies, and three months in the rat reproductive bioassays, even a smaller fraction, approximately 40 percent, of the cumulative administered dose (rats) can be estimated to elicit adverse reproductive effects in rhesus monkeys, i.e., the latter species exhibits 2-3 fold greater sensitivity than the rodent species. The cumulative dose response analysis places the sequence of health concerns - reproductive, developmental and carcinogenic in perspective.

A further concern arose from the experimental observations of Moore et al which showed that high levels of the unmetabolized dioxin congener, 2,3,7,8-TCDD, were excreted in milk and that each rat pup actually received a higher dose during the first week after birth than was administered initially to the mother. (11) This study revealed that while TCDD crosses the placenta in the rat, exposure of the offspring occurs mainly through nursing. Thus the maternal milk pathway is a significant pathway affecting neonatal development in rats. Dioxins have been detected in human breast milk but there is no evidence to link dioxin exposure through nursing to human neonatal developmental toxicity. It was concluded that the animal data on reproductive effects can be used to derive a total dose limit to human exposure in 2,3,7,8 - TCDD equivalents. Thus, the reported LOEL 1.8 ng/kg/day

in the rhesus monkey study was reduced by an Uncertainty Factor of 1000 to estimate the dose limit at 1.8 pg/kg/day.

DOSE APPORTIONMENT BY MEDIUM

Since cumulative dose is relevant to dioxin effects and since there are multiple media and sources of dioxins, it was necessary to consider an apportionment approach.

Assumption. Considering the multi-media nature of dioxin exposure, the health-based limit of 1.8 pg/kg/day (based on reproductive effects as most sensitive response) should be apportioned by medium of exposure and an allowable level established for each medium. This apportionment considers potential background exposures to be significant.

Rationale. Although the background dioxin levels in the environment contribute to the total human body burden, this information was not factored in the calculation of the health-based total dose limit of 1.8 pg/kg/day. Thus the limit reflects the total theoretical permissible daily dose of dioxins from all media of exposure, including background exposure. It represents the maximum daily dose that should not be exceeded to assure that no adverse health effects occur over a lifetime of exposure to dioxins. Therefore when assessing only one of the several possible exposure media, it is necessary to apportion the health-based limit to account for other potential exposures.

The first step in apportioning multi-media exposure of humans to dioxins was to estimate the background contribution to total dioxin exposure. The average daily intake of dioxin can be estimated using a linear, one compartment model: (3)

Background Dose Rate = Body Burden x In 2 / half-life (ng/kg/day) (days)

Assuming that a human weighs 60 kg, has 20 percent fat, and has 7 ppt dioxin in fat (ng/kg), (12) then the body burden of dioxin is 84.0 ng. The half life is assumed to be 5.8 years (2120 days) (13) and the dose rate is estimated to be approximately 0.45 pg/kg/day. Travis and Hattemer-Frey estimated through half-life modeling and 70 kg assumption that human exposure to 2,3,7,8-TCDD is about 0.4 pg/kg/day. (3) An EPA calculation showed a range of estimates of daily intake of 2,3,7,8 - TCDD between 0.04 to 0.51 pg/kg/day. The daily dioxin intake value used by DHS is in reasonable agreement with those reported above. This background exposure at 0.45 pg/kg/day (direct and indirect) represents 25 percent of the health-based limit of 1.8 pg/kg/day.

Estimates of the relative contributions from air, food, water, and soil to the daily human exposure to dioxins were calculated from literature data. The available data on dioxin exposures were reviewed, in particular the Federal Ontario dioxin exposure assessment document. (14) This document assumed that dioxins in the Ontario environment are principally from incineration processes. Based on concentrations and contact rate the relative contributions were estimated to be: air (60%), water (5%), soil (5%), and food (30%). DHS adjusted this apportionment to account for (i) potential beef and milk exposure, and (ii) sensitive sub-groups (infants and children - milk pathway). Thus DHS estimated the relative contribution to be: air (40%), water (5%), soil (5%), and food (50%) in the Connecticut environment.

The relative source contribution of 40 percent from the air medium was

derived from the worst case exposure assessment of the Ontario environment. $^{(14)}$ The Ontario data represent the measurements of stack air (there was no ambient air data) and the levels found in samples of fish, pork, poultry products, drinking water, human fat. and the soil in the vicinity of an incinerator. The Canadian assessment used (i) an estimated maximum annual average ambient air concentration of 8.4 pg/m 3 TCDD equivalents (60% apportioned intake); (ii) for water, a concentration of 0.002 ng/L TCDD equivalents (5% intake); (iii) for soil, a level of 81.1 pg/g TCDD equivalents (5% intake); and (iv) for food consisting of fish, poultry, pork and eggs, 29.6 pg/g (30% intake). No meat, milk and fruit analyses were provided in the Ontario analysis, consequently, the Connecticut food apportionment was adjusted to 50%, and air to 40%.

For the air medium (40% apportionment), the matrix was considered to include both vapor and particulate phases (the ambient air quality standard takes into account both phases). Dioxins and furans released from a variety of combustion sources have been shown to exist in vapor and particulate phases (15). The vapor phase, as well as the particulate phase (assumed to be 100 percent in the respirable range) represent an inhalation hazard. Moreover, volatilization from the background and atmospheric transport of these semivolatile organics can potentially add to inhalation exposure. Based on sampling data and modeling, 2,3,7,8-TCDD in the urban air has been reported to exist in the particulate phase between 40 and 80 percent (16) whereas the octaisomer is 100 percent particle bound.

The vapor phase half-life through photolysis has been reported to be under six hours, and for the particulate phase the half-life is several hundred hours. At locations close to the spectrum of combustion sources exposure to vapor phase dioxins via inhalation can occur, in addition to direct inhalation of the respirable particulate phase. The background levels of dioxins in the vicinities of resource recovery facilities in Connecticut have been measured. The values (48 hr average) are: Mean = $0.045 \text{ pg/m}^3 \pm 0.77$, Maximum = 0.719 pg/m^3 , Range = $0.004 \text{ to } 0.719 \text{ pg/m}^3$ dioxin equivalents, and N = 130. Fish samples (background monitoring) showed that the levels ranged from 0.23 to 8.95 pg/g for TCDF, and from a method detection limit of 0.05 to 6.15 pg/g for 2.3.7.8-TCDD. The monitored background data for Connecticut, although limited, indicate that both the atmospheric and food chain exposures are potentially significant human exposure pathways.

The settling velocity is an important factor in determining the signifcance of exposure pathways. Whereas the inhalation exposure pathway contributes to a constant absorbed dose (1 pg/m³ x 20 m³/day = 20 pg/day)
from the vapor and particulate phases (this inhaled dose is independent of
settling velocity), the dose estimate for the indirect food chain pathway is
dependent on the settling velocity assumption. For example the Hart analysis (1) showed that the food chain contribution increased with increasing
settling velocity from 56, 80, to 98 percent for settling velocities of
0.0003, 0.001, and 0.01 m/sec respectively, for the same ambient concentration.

The question arises as to the appropriate settling velocity to use in dose calculation. Travis et al's 1987 analysis used a settling velocity of 0.0023 m/sec and 100 percent particle-phase distribution to estimate the food pathway's contribution to total daily intake (98 percent). (3) On the other hand, a settling velocity of 0.001 m/sec was used in the Hart document to estimate the food chain contribution (80 percent). (1) Additionally, if the particle phase distribution were to be factored into the calculation (40 to 80 percent for 2,3,7,8-TCDD) then the food chain pathway percent contribution would be in the 56 to 72 percent range. Connecticut's 40 percent relative source contribution from air, and 50 percent from food to the daily

dioxin intake are consistent with an average settling velocity of 0.001 m/sec, and 60/40 particle-vapor phase distribution assumptions. It should be emphasized that the exposure assessment and dose apportionment for the Connecticut assessment are based on the assumption that direct inhalation intake is from vapor and particulate phases, and the indirect intake is primarily from the particulate phase. The apportioned daily dosing rate associated with air exposure is 0.72 pg/kg/day (40 percent of 1.8 pg/kg/day). The equivalent dioxin concentration in ambient air is 2.2 pg/m^3 ($0.72 \text{ pg/kg/day} \times 60 \text{ kg/20 m}^3 \text{ per day}$). The calculations and conversions are based on the dose limit of 1.8 pg/kg/day.

DEP RISK MANAGEMENT

The DEP considered the DHS assessment, the Hart assessment and their factors in the risk management phase.

Connecticut DEP reviewed a range of health-based estimates for a dloxin equivalent AAQS - 0.1 to 2.2 pg/m³. The lower bound value (0.1 pg/m³) comes from the initial Hart analysis and the upper bound, from the DHS analysis. DEP decided to reduce by a factor of 2.2 the highest concentration in the range and derived a level of 1 pg/m³. This dloxin equivalent concentration of 1 pg/m³ was proposed and adopted as the AAQS.

The DEP management decision to apply an additional safety factor of 2.2 was based on the desire for an added margin of protection against potential carcinogenic and immunotoxic effects and on operating considerations. This safety factor assured that no exceedences of the health-based limit would occur through indirect and background exposures. According to DEP, the decision considered other management inputs, such as monitoring and enforcement as well as analytical and statistical considerations.

The following analysis explains the health rationale for the 2.2 factor and shows how the standard of 1 pg/m 3 is protective of human health: At the maximum ambient dioxin concentration of 1 pg/m³ from all combustion sources, the daily inhaled dose can be estimated to be 0.33 pg/kg/day (60 kg human body weight and 20 m³ air breathed in a day). This calculated dose represents about 18 percent of the health-based limit of 1.8 pg/kg/day. The Hart document provided an estimate of the indirect contribution from 1 pg/m³ air dioxin concentration to be about 1.0 pg/kg/day (100 percent particle phase assumption and 0.001 m/seg settling velocity). This intake is 55 percent of the limit. Adjusting for 40 to 80 percent particle phase, the indirect dose can be estimated to be 0.4 to 0.8~pg/kg/day (22 to 44 percent of the limit). Additionally the background can potentially contribute to an estimated 0.45 pg/kg/day (25 percent of the limit). Thus, the direct (inhaled), indirect, and background intakes can contribute up to 65 to 98 percent of the health-based limit. If the 2.2 safety factor is not applied to the 2.2 pg/m^3 estimate, a potential doubling of the dose would occur and the target limit would be exceeded. A higher safety factor (10) was considered not necessary since DEP proposed to regulate individual sources through an emission standard that ensures each source will have an insignificant impact on ambient air. The dioxin AAOS 1 pg/m3 is thus considered to be protective of public health.

DIOXIN EXPOSURE AND CANCER RISK

The potential cancer risks from chronic exposure to dioxins via ingestion (indirect pathway) and inhalation (direct pathway) were evaluated. The calculation used the standard approach that the product of the exposure dose (pg/kg/day) and the potency value represents the potential upperbound risk.

Ingestion Risk. The ingestion risks from the indirect exposure pathway were estimated for three deposition scenarios. The calculation assumed that 100, 80, or 40 percent of the dioxin in the ambient air is in the particle phase and that the settling velocity is 0.001 m/sec. The estimated doses, 1.0, 0.8, and 0.4 pg/kg/day were multiplied by the oral potency values to calculate the potential upperbound risks, as shown in Table 1.

Inhalation Risks. Inhalation risk assessment for the direct exposure pathway focussed on the administered dose via inhalation, 2,3,7,8,-TCDD's potency via inhalation, and the effect of the matrix factor on dioxin's potency.

Administered Dose. The concentration in the ambient air (pg/m^3) and the contact rate $(20~m^3/day)$ for a human body weight assumption (60~kg), and 100 percent pulmonary absorption determined the administered dose (pg/kg/day) via inhalation. A second calculation considered the particle/vapor nature of the airborne dioxins as well as the matrix effect and used an absorption factor of 50 percent to calculate the administered dose.

<u>Inhalation Potency and Matrix Effect</u>. Since 2,3,7,8-TCDD's potencies for the vapor and particulate phases via inhalation are not known, the oral potency values are used to predict the inhalation risk. This is considered a conservative approach for the following reasons:

Dioxin's potency estimates are based on the administered dose. In the lifetime feeding study the rats were given a diet mixed with dioxin dissolved in acetone matrix. (9) The bioavailability of dioxin in this matrix is reported to be 85 percent, compared with the values, 25 to 50 percent for the soil matrix, (17, 18) and 1 to 4 percent for the flyash matrix. (19) These bioavailability values are for oral/gastrointestinal absorption. The absorption values for the soil and flyash matrix indicate that considerably higher doses, 2 to 20 times higher than the dose in acetone matrix are required to produce the same dioxin concentration in the liver and elicit a tumor response. Such a shift in the dose/response curve relative to the matrix effect would predict a lower potency estimate for ingested dioxin. Thus the use of the oral potency values (acetone matrix) to predict the inhalation risk, particularly for inhaling particle bound dioxins, is considered conservative. Table 1 presents the estimated inhalation risks for 100 and 50 percent absorption assumptions.

Table 1. Dioxin Exposure and Upperbound Cancer Risk Estimates

| | | 10-6 | .0-6 Risk Specific Dose (fg/kg/day) ** | | |
|-------------|------------|----------------------|--|--|--|
| Dose * | Assumption | EPA | C.L | FDA | EPA *** |
| (pg/kg/day) | | 6 | 36 | 60 | 100 |
| Direct | | | | • | |
| 0.33 | 100% Abs | 5.5x10 ⁻⁵ | 9×10-6 | 5.5x10-6 | 3.3x10 ⁻⁶ |
| 0.17 | 50% Abs | 2.8x10 ⁻⁵ | 4.5x10 ⁻⁶ | 2.8x10-6 | 1.7x10 ⁻⁶ |
| Indirect | | | | - - | . 5 |
| 1.00 | 100% part | 1.7×10 ⁻⁴ | 2.8×10 ⁻⁵ | 1.6x10 ⁻⁵ | 1.0x10 ⁻⁵ 8x10 ⁻⁶ |
| 0.80 | 80% part | 1.3x10 ⁻⁴ | 2.2x10 ⁻⁵ 1.1x10 ⁻⁵ | 1.3x10 ⁻⁵ 7x10 ⁻⁶ | 8x10 ° 4x10−6 |
| 0.40 | 40% part | 7x10 ⁻⁵ | 1.1XIO 2 | /X10 ° | 4x10 ° |

^{*} The dose was estimated for a dioxin concentration of 1 pg/m^3 , a breathing rate of 20 m^3 /day and a human body weight of 60 kg.

*** Proposed potency estimate.

^{**} Femtogram (one quadrillionth of a gram).

Depending on the scientific assumptions used and the estimate of the carcinogenic potency of dioxin, the range of upperbounds on total risk from indirect and direct exposure to 1 pg/m³ ranges from 2 x 10^{-4} (5.5 x $10^{-5} + 1.7$ x 10^{-4}) to 6 x 10^{-6} (1.7 x $10^{-6} + 4$ x 10^{-6}). In the scientific judgement of DHS, the risk was estimated to be at the lower end of the range or 6 x 10^{-6} . A potential risk in the 10^{-6} range is considered acceptable for an aggregate air standard for all sources of dioxin emissions. However, for individual Resource Recovery Facilities, the potential cancer risk from ambient impact is even lower and is in the 10^{-7} range. The background estimate (0.45 pg/kg/day) represents a risk in the $10^{-5} - 10^{-6}$ range, depending upon the assumptions used.

DISCUSSION AND CONCLUSION

Connecticut is the first state in the country to adopt a dioxin AAQS that protects the public health from the combined effects of all sources of dioxin emissions. The AAQS is an aggregate standard and is different from the "standards" of other states which are in fact only maximum allowable impacts for individual RRFs. According to Connecticut DEP, "no resource recovery facility in the state is predicted to have an ambient impact of more than $0.037~pg/m^3$ dioxin equivalents." (2) This maximum predicted impact for each RRF represents about 4 percent of the AAQS, and is consistent with the limits imposed by other states (Massachusetts 0.15, Pennsylvania 0.3, Rhode Island 0.02 to 0.2, and New Hampshire 0.09 to 0.27 pg/m³). The predicted maximum impact for each RRF in the state represents a potential upperbound carcinogenic risk in the 10^{-6} to 10^{-7} range. No adverse reproductive and immunological effects are expected to occur at this impact level. The calculated dose for 0.037 pg/m³ impact level (direct and indirect) is 0.049 pg/kg/day and it represents about 3 percent of the health-based limit, compared with the background's 25 percent. Clearly, there is a need to identify the sources contributing to the considerable background intake, and minimize such exposure.

The non-source specific approach used in the risk assessment is a departure from incinerator-specific risk assessments. Appropriately, this approach takes into account the body burden and daily dose from all media and sources as well as the background exposures when estimating a total daily dose and comparing with the target dose limit. The target dose limit assumption facilitated apportioning the dose by media. While developing a rationale for the 40 percent air apportionment, it became apparent that the risk assessment is sensitive to the settling velocity assumption used. Inhalation (44 percent) and meat/milk ingestion (56 percent) are significant exposure pathways for a minimum particle settling velocity (0.0003 m/sec) assumption. (1) The relative significance of the inhalation exposure decreases as the settling velocity increases. At the settling velocity 0.01 m/sec, the indirect food chain pathway dominates (98 percent) although the concentration of dioxins in the air is the same. Therefore, risk assessments of this type should estimate exposures based upon several settling velocities as a means of estimating a range of potential exposures. This is particularly necessary since the location of the plant affects the settling velocity. This type of analysis will help the risk manager to assess inhalation exposure separate from indirect multiple pathway exposure, if desired. A further improvement in dioxin risk assessment would come from the knowledge of vapor/particulate phase distribution of dioxins in ambient air. This information would improve the analysis of the indirect exposure pathways, since the deposition of dioxins from the ambient air has been shown to be particle phase dominated. (16)

REFERENCES

- F. C. Hart Associates, "Multiple Pathway Human Exposure and Health Risk Assessment of Polychlorinated Dibenzo-p-Dioxins and Polychlorinated Dibenzofurans from Municipal Solid Waste Incinerators," Prepared for State of Connecticut, Department of Health Services, February, 1987.
- Connecticut Department of Environmental Protection (DEP), "Basis for Standards and Procedures and Response to Comments on Proposed Resource Recovery Regulations (Air Pollution Provisions)," (1988).
- C. C. Travis and H. A. Hattemer-Frey, "Human Exposure to 2,3,7,8-TCDD," Chemosphere 16, 2331-2342 (1987).
- C. C. Travis and H. A. Hattemer-Frey, "A Perspective on Dioxin Emissions from Municipal Solid Waste Incinerators," Risk Analysis 9, 91-97 (1989).
- 5. Environmental Protection Agency, "Health Assessment Document for Polychlorinated Dibenzo-p-dioxins," Office of Health and Environmental Assessment, May 1984.
- 6. F. J. Murray, F. A. Smith, K. D. Nitschke, C. G. Humiston, R. J. Kociba, and B. A. Schwetz, "Three-Generation Reproduction Study of Rats given 2,3,7,8-Tetrachlorodibenzo-p-dioxin in the Diet," Toxicology and Applied Pharmacology 50, 241-252 (1979).
- J. R. Allen, D. A. Barsotti, L. K. Lambrecht, and J. P. Van Miller, "Reproductive Effects of Halogenated Aromatic Hydrocarbons on Nonhuman Primates," <u>Annals of New York Academy of Sciences</u> 320, 419-425 (1979).
- 8. I. C. T. Nisbet and M. B. Paxton, "Statistical Aspects of three generation studies of the reproductive toxicity of 2,3,7,8-TCDD and 2,4,5-T," The American Statistician 36, 290-298 (1982).
- 9. R. J. Kociba, D. G. Keyes, J. E. Beyer, R. M. Carreon, E. E. Wade, D. A. Dittenber, R. P. Kalnins, L. E. Frauson, C. N. Park, S. D. Barnard, R. A. Hummel, and C. G. Humiston, "Results of a Two-Year Chronic Toxicity and Oncogenicity Study of 2,3,7,8-TCDD," Toxicology and Applied Pharmacology 46, 279-303 (1978).
- 10. T. H. Umbreit, E. J. Hesse, and M. S. Gallo, "Reproductive Toxicity in Female Mice of Dioxin-Contaminated Soils from a 2,4,5 Trichlorophenoxyacetic Acid Manufacturing Site," Archives of Environmental Contamination and Toxicology 16, 461-466 (1987).
- 11. J. A. Moore, M. W. Harris, and P. W. Albro, "Tissue Distribution of ¹⁴C Tetrachlorodibenzo-p-dioxin in Pregnant and Neonatal Rats," Toxicology and Applied Pharmacology 37, 146-147 (1976).
- 12. D. G. Patterson, J. S. Holler, S. J. Smith, J. A. Liddle, E. J. Sampson and L. L. Needham, "Human Adipose Data for 2,3,7,8-TCDD in Certain U.S. Samples," Chemosphere 15, 2055-2060 (1986).
- 13. H. Poiger and C. Schlatter, "Pharmacokinetics of 2,3,7,8 TCDD in Man," Chemosphere 15, 1489-1494 (1986).

- 14. Ontario Ministry of The Environment, "Scientific Criteria Document for Standard Development No. 4-84 - Polychlorinated Dibenzo-p-Dioxins and Polychlorinated Dibenzofurans," Ministry of The Environment, Toronto, March, 1986.
- 15. T. F. Bidleman, "Atmospheric Processes," Environ. Sci. Technol 22, 361-367 (1988).
- 16. T. F. Bidleman, "Gas-Particle Distribution and Atmospheric Deposition of Semi Volatile Organic Compounds," Presented at the EPA/ORNL Workshop on Risk Assessment for Municipal Waste Combustion, June 8-9, 1989.
- 17. T. H. Umbreit, E. J. Hesse, and M. S. Gallo, "Bioavailability of Dioxin in Soil from a 2,4,5-T Manufacturing Site," Science 232, 497-499 (1986a).
- 18. T. H. Umbreit, E. J. Hesse, and M. S. Gallo, "Comparative Toxicity of TCDD Contaminated Soils from Times Beach, Missouri, and Newark, New Jersey," Chemosphere 15, 2121-2124 (1986b).
- 19. M. Van den Berg, K. Olie, and O. Hutzinger, "Uptake and Selective Retention in Rats of Orally Administered Chlorinated Dioxins and Dibenzofurans from Fly Ash and Fly Ash Extract," Chemosphere 12, 537-544 (1983).

Letter to the New England Journal of Medicine [September, 1990]

To the Editors: In their January 11 article Needleman et al. 1 report strikingly large effects of low lead levels on several late adolescence outcomes. For example, an estimated 7.4-fold increased odds of school failure was attributed to childhood lead dentin levels above 20 ppm. Such massive effects sizes contrast sharply with results of other studies relating low lead level to earlier developmental outcomes 2-4. The authors argue that the estimated effects represent causal relationships because their analysis controlled for ten sociodemographic covariates. This conclusion of causality may be premature, however, because the covariate set did not include measures of the quality of child care (i.e., parental responsitivity, involvement with the child, provision of books, suitable playthings, etc.), a primary confounder in previous studies of developmental lead effects. Thus the reported lead effects may be partly due to spurious association induced by variations in the caretaking environment.

Indices of child care quality such as the HOME ⁵ and the CLL ⁶ have repeatedly been found to be strongly related to lead level in poor and working class children ^{2,4,7,8}. Quality of child care is also strongly associated with developmental outcome ³, including school performance through adolescence ¹⁰. These confounding effects are conceptually distinct from and only partly accounted for empirically by socio-demographic variables such as maternal IQ and parental education ¹¹, which were included as covariates by Needleman et al. The fact that none of the reported lead effects were attenuated by inclusion of their covariates, as is usually the case in observational studies of low lead levels, indicates that confounders such as child care may not have been fully controlled.

On another matter, the present report is a follow-up of a 1979 report 12 which troubled reviewers 13 , in part, because many cases were excluded after testing. In a written response to the review 14 , Needleman reported data indicating that a key IQ analysis was substantially affected by 16 of the

excluded children with excess lead, or plumbism: Prior to exclusion, with N = 187, the lead effect \underline{t} = -1.51 (\underline{p} = .133, 2 - sided); after exclusion, with N = 171, \underline{t} = -2.56 (\underline{p} = .011). This suggests the presence of high IQ's in the plumbism group. In the present follow-up report, the previously excluded cases who agreed to participate were incorporated in the analysis, including, in separate descriptive summaries, ten of the plumbism cases. Five of these plumbism cases had reading disabilities, and three out of seven failed to graduate high school. These high proportions of adverse outcomes seem to corroborate the hypothesized lead effect. However, in view of the apparently contradictory IQ data described above, a summary of the IQ scores of all 16 plumbism cases would be helpful in assessing the implications of the findings.

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References

- Needleman HL, Schell A, Bellinger D, Leviton A, Allred EN. The long term effects of exposure to low doses of lead in childhood. N Eng J Med 1990;322: 83-8.
- 2. McMichael AJ, Baghurst PA, Wigg NR, Vimpani GV, Robertson EF, Roberts RJ. Port Pirie cohort study: Environmental exposure to lead and children's abilities at the age of four years. N Eng J Med 1988;319: 468-75.
- 3. Fergusson DM, Fergusson JE, Horwood LJ, Kinzett NG. A longitudinal study of dentine lead levels, intelligence, school performance and behaviour II. Dentine lead and cognitive ability. J Child Psychol Psychiatry 1988;29:793-809.
- 4. Ernhart CB, Morrow-Tlucak M, Wolf AW, Super D, Drotar D. Low level lead exposure in the prenatal and early preschool periods:

 Intelligence prior to school entry. Neurotoxicol Teratol 1989;11:
 161-170.
- 5. Caldwell BM, Bradley R. Home Observation for the Measurement of the Environment. Unpublished manuscript. Little Rock: Univ of Arkansas at Little Rock, 1984.
- 6. Polansky NA, Borgman RD, De Saix C. Roots of Futility. San Francisco: Jossey-Bass, 1972.
- 7. Dietrich KN, Krafft KM, Pearson DT, Harris LC, Bornschein RL, Hammond PB, Succop PA. Contribution of social and developmental factors to lead exposure during the first year of life. Pediatrics 1985:75:1114-9.

- 8. Hunt TJ, Hepner R, Seaton KW. Childhood lead poisoning and inadequate child care. Am J Dis Child 1982;136:538-542.
- 9. Bradley RH, Caldwell BM, Rock SL, Ramey CT, Barnard KE, Gray C,
 Hammond MA, Mitchell S, Gottfried AW, Siegel L, Johnson DL. Home
 environment and cognitive development in the first 3 years of life: A
 collaborative study involving six sites and three ethnic groups in
 North America. Dev Psychol 1989;25:217-35.
- 10. Hess RD, Holloway SD. Family and school as educational institutions.

 In: Parke RD, ed. The Family. Chicago: Univ. Chicago Press, 1984.
- 11. Schroeder SR, Hawk B. Psycho-social factors, lead exposure and IQ. In: SR Schroeder (Ed.) Toxic Substances and Mental Retardation: Neurobehavioral Toxicology and Teratology. Washington, D.C.: AAMD Monograph Series, 1987
- 12. Needleman HL, Gunnoe C, Leviton A, Reed R, Peresie H, Maher C, Barrett P. (1979). Deficits in psychological and classroom performance in children with elevated dentine lead levels. N Eng J Med 1979;300: 689-95.
- 13. US Environmental Protection Agency. Independent peer review of selected studies concerning neurobehavioral effect of lead exposures in nominally asymptomatic children: Official report of findings and recommendations of an interdisciplinary expert review committee. (EPA-600/8-83-028A).
- 14. Needleman HL. Appendix to the ECAO critique. Unpublished manuscript, on file with the Environmental Protection Agency, 1984.

"LEGISLATIVE & REGULATORY ASPECTS OF RISK"

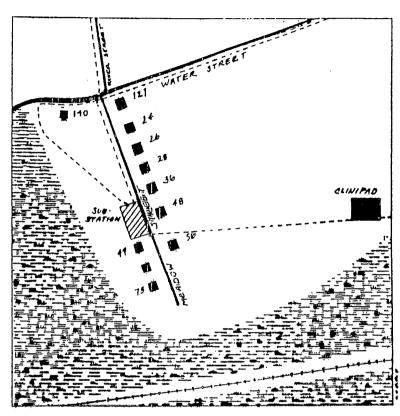
David Brown

ANNALS OF RADIATION

CALAMITY ON MEADOW STREET

N a Friday evening in mid-January of this year, Edna and Robert Hemstock received a visit at their home, in Guilford, Connecticut—a town on Long Island Sound about fourteen miles east of New Haven-from their friends Loretta and Fred Nelson. who also live in Guilford. Edna Hemstock, a vivacious woman in her middle forties. who is Robert's second wife. works as an office manager for a manufacturing firm; Robert Hemstock, a redhaired, forty-nine-year-old man of Irish ancestry, is a free-lance consultant for machinery design and product development. Loretta Nel-

son, a slender, sombre woman in her early forties, works at a nearby electronics plant; and Fred Nelson, an affable, wiry, gray-haired man of fiftyfour, is an oil-burner serviceman. The two couples had become acquainted a year or so earlier, when the Nelsons' seventeen-year-old daughter, Joyce, and Charles Hemstock, Robert's twenty-year-old son by his first marriage, who had been living together in the Nelsons' house, on Meadow Street, learned that Joyce was pregnant. This was a cause of some concern to both sets of prospective grandparents, because in 1982 Joyce, who is called Missy by her family and friends, had been found to be suffering from the extremely rare combination of glomerulonephritis—a disease of the kidney capillaries, which



ounce girl. Sitting at the Hemstocks' kitchen table nearly three months later, Loretta Nelson made a point of remarking on how lucky they were to be grandparents, considering the threat that Joyce's kidney ailment had posed to her pregnancy. She added, "And considering all the other illness there's been on Meadow Street," which caused Dob Hemstock to sit up and take notice.

"That was the first time I'd heard anything about a lot of illness on Meadow Street," Hemstock said recently. "Edna and I had visited the Nelsons on several occasions while Missy was pregnant, and we had met their neighbor Suzanne Bullock, whose seventeen-year-old daughter, Melissa, had been operated on for brain cancer earlier that year, but neither of us knew

glomerulor lipodystroph but that he might be the vulnerability type of envir She went on and Fred ki case of either one's fami minding the Melissa Bul next door. had develop she told the Walston III at 36 M - dc young .__ 1, brain tumor teen-seventi living at 4 house next of

side. She then said father, Jonathan W was born at 36 Mead-there most of his life, brain cancer in 1975. a woman who had liv—three houses over—asthma, in 1989, had tumor in the early nir

Hemstock was flable heard, because which runs north to mates at a salt mare Guilford and Long only about two bonds long and has on. Lir said, "Good God, Loize how odd it is to brain cancer on one s

Loretta replied the

STATE OF CONNECTICUT

DEPARTMENT of HEALTH SERVICES





PUBLIC HEALTH EDUCATION SECTION 150 Washington St. Hartford, Connecticut 06106 Telephone 566-4800

FOR IMMEDIATE RELEASE

August 22, 1989

CONTACT:

Matthew Cartter, M.D. 566-5058

David Brown, Sc.D. 566-8167

CAUTION URGED WHEN USING INSECT REPELLENTS

Health officials in Connecticut, New York and New Jersey are advising people using insect repellents containing the chemical DEET on exposed skin to exercise caution to avoid overexposure and possible reactions. Insect repellents should be used to prevent insect-borne problems, but they should be used with care.

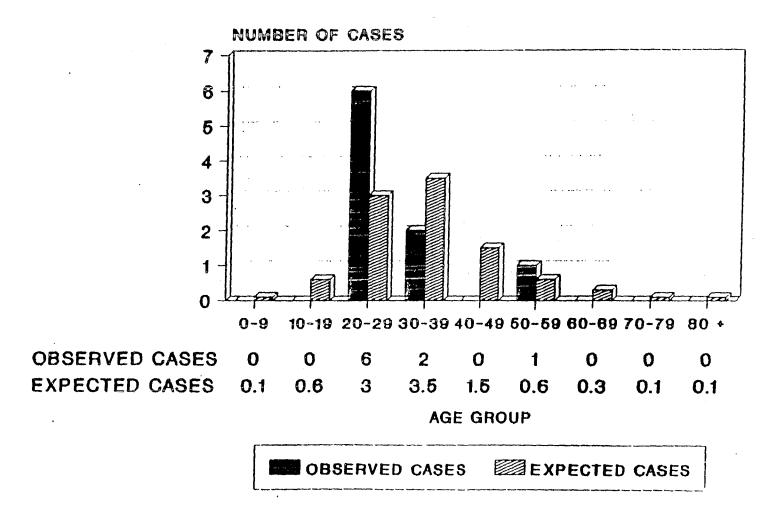
The advisory comes from the Connecticut Department of Health Services, the New York Department of Health, and the New Jersey Department of Health.

Public concern about Lyme disease, which is transmitted by infected deer ticks, and concern about this year's large mosquito population may cause some people to apply on the skin excessive amounts of insect repellents with DEET (N,N-diethyl-m-toluamide) for prolonged periods of time, thus increasing the chance of adverse reactions.

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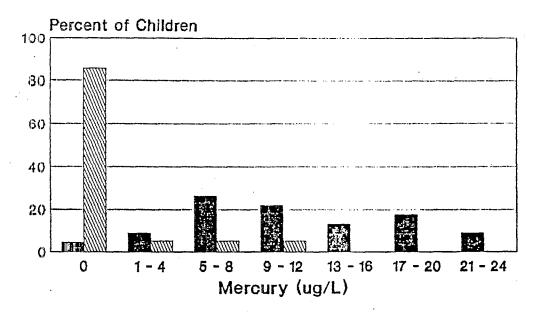
figure 7

OBS VS. EXP TESTICULAR CANCER CASES SOUTHINGTON, CT 1979 TO 1988





Mercury in Urine, Waterbury, CT, 1990 Exposed v. Control Children



Index Child: Mercury = 680 ug/L, 24-Hr

ISSUES ADDRESSED BY DATABASE SEARCHES

- . METHODS TO CHELATE AND MONITOR CHILDREN EXPOSED TO HIGH LEVELS OF MERCURY DURING AN ACUTE EXPOSURE INCIDENT
- . IDENTIFICATION OF HUMAN HEALTH EFFECTS FROM DEET OVER-EXPOSURE TO INFORM STATE CONSUMERS
- . ESTABLISHING PLAUSIBILITY OF BLADDER AND TESTICULAR CANCER FROM OVEREXPOSURE TO KNOWN CONTAMINANTS
- . DEFINING ENVIRONMENTAL FATE OF HAZARDOUS MATERIALS TO ASSESS EXPOSURE PATHWAYS FROM ACCIDENTAL RELEASES AND IDENTIFIED WASTE SITES
- . TOPIC SEARCHES TO KEEP UPDATED ON LATEST DEVELOPMENTS IN RISK ASSESSMENT, PHARMACOKINETICS, CLUSTER INVESTIGATIONS AND OTHER RELATED SCIENCES

EXAMPLES OF NLM DATABASE SEARCHES:

- 1. LITERATURE SEARCH FOR DEET AND ITS HUMAN HEALTH EFFECTS.
- 2. CHEMICALS CAUSING BLADDER AND TESTICULAR CANCER IN HUMANS.
- 3. INFORMATION ON HEALTH EFFECTS AND ENVIRONMENTAL FATE FOR CHEMICALS (TRI):
 - RELEASED IN WALLINGFORD TO EVALUATE WHETHER PUBLIC HEALTH THREAT EXISTS.
- 4. LITERATURE SEARCH ON INSECT REPELLENTS.
- 5. PHARMACOKINETICS AND RISK ASSESSMENT LITERATURE SEARCH (TO KEEP CURRENT AND TO UPDATE LATEST TECHNIQUES.)
- 6. GROUND AND SURFACE WATER CONTAMINATION
 - T-BUTANOL
 - NICKEL
- 7. AIR CONTAMINATION
 - DIOXIN
 - HCL
 - PCB
- 8. FISH CONSUMPTION SURVEYS

CONNECTICUT'S DIOXIN STANDARD*

1. Legislative mandate.

SEARCH (TO KEEP CURRENT AND TO UPDATE LATEST TECHNIQUES.)

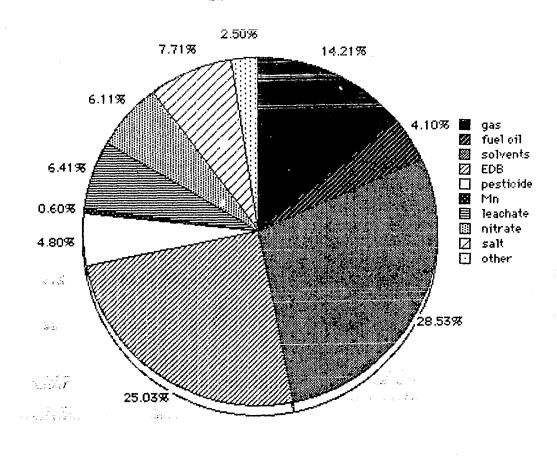
4. Dose apportionment: The Contract GETAN BURGER GRA CHICAR

5. Non-cancer endpoints.

*ambient air quality standard for dioxins at 1 pg/CuMeter TCDD equivalents

A FITH ECONSUMPTION PORTION

Contembrated wells in Connection: 1,368 wells



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RESULTS OF 1989 ESURAC "SUMMARY OF STATE AND PUBLISHED WANTER SCANDARDS AND GUIDELINES"

| | SHACIDAC | CONTAMINANTS | Total. | CONTAMUSANTES | CONSIDERING | USE CANCER | ADD'L MONITORING | GULDELUNES |
|--|-------------|--|--------|---------------|----------------|---------------|---------------------|------------|
| | 579. | CUID. | Sud. | CUIID. | COLD. CR. STD. | RLSK LVLS. | | ENFORCED |
| | | | | | | | | |
| number of States | 19 | 22 | 4 | 6 (1) | 77 | 20 | 19 | 18 |
| PERCHNU: OF: 43: STATES: IN: SURVEY: | 44% | 51X | 972 | 142 | 63X | 47% | 44% | 42% |
| PERCENT: OF 50 | 38% | ************************************** | 8% | 1127 | 54% | 40Z | 38% | 36% |
| | | | | | | | | |

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1431

METHYL-TERT-BUTYL ETHER (MTBE)

AGENCIES HAVING GUIDELINES OR STANDARDS

| AGENCY | STANDARDS CURRENT FUTURE (UG/L) (DATE) | GUIDELINES CURRENT FUTURE (UG/L) (DATE) NOTE |
|----------------------------------|--|--|
| CONNECTICUT | | 100 |
| ENVIRONMENTAL PROTECTI AGENCY | ОИ | 9/90 |
| MASSACHUSETTS | | 50 |
| MAINE | | 50 |
| NEW HAMPSHIRE | | 200 |
| RHODE ISLAND | | 50 |
| VERMONT | 40 | |

STATES REQUESTING EPA TO SET STANDARD FOR MIDE UNDER SAFE DRINKING WATER ACT:

CONNECTICUT
MASSACHUSETTS
MAINE
NEW HAMPSHIRE
NEW JERSEY
NEW MEXICO

3157I

| The second secon | TOTAL NUMBER | ESTIMATED TOTAL |
|--|--------------|-----------------|
| CONTAMINANT | OF WELLS | POPULATION |
| ∰.\$ | 202 | 113) |
| FUEL OIL | 59 | 3213 |
| SOLVENTS | 406 | 195993 |
| EDB | 356 | 37643 |
| PESTICIDE | . 69 | 12288 |
| Mn | 9 | 29 |
| LEACHATE | . 91 | 671 |
| NITRATE | 87 | 327 |
| SALT | 110 | 11207 |
| OTHER | 35 | 906 |

TOTAL NUMBER OF WELLS = 1,368

ESTIMATED TOTAL POPULATION = 255,282



STATE OF CONNECTICUT

DEPARTMENT OF HEALTH SERVICES

VOLATILE ORGANICS AND INORGANICS ACTION LEVELS April 1990

The Department of Health Services uses Public Health Code Regulation 19-13-B102 and the following list to determine the potability of drinking water supplies. The concentrations given are action levels and are expressed in micrograms per liter.

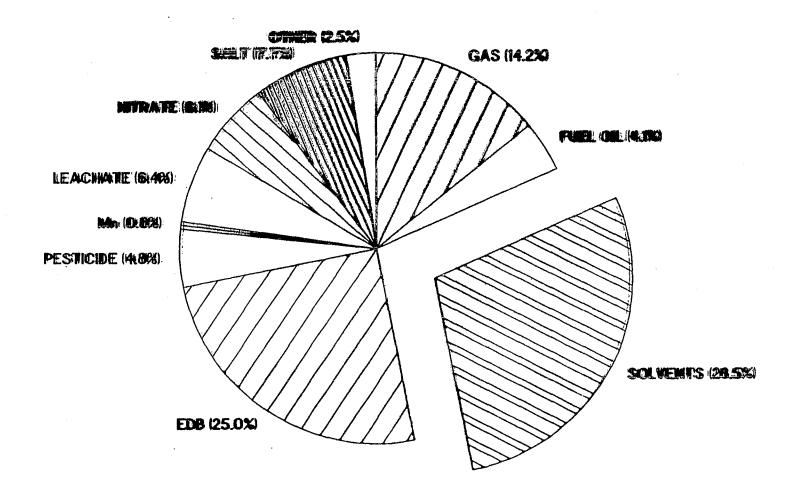
| COMPOUND | ACTION LEVEL | |
|--|-----------------|-----|
| The state of the s | (Micrograms/11) | er) |
| | | · |
| Acrylonitrile | 35 | A |
| Benzene | 1 | · Č |
| Carbon tetrachloride | 5 | |
| 1,2-Dibromoethane (EDB) | 0.1 | В |
| Para-Dichlorobenzene | 75 | c |
| 1,2-Dichloroethane (EDC) | 1 | 3 |
| 1,1-Dichloroethylene | 7 | С |
| 1,2-Diehlerepropane | 5 | В |
| 1,3-Dichloropropene | 10 | В |
| Dieldrin | 0.01 | В |
| 1,4 Dioxane | 20 | A |
| Ethylene Glycol | 100 | A |
| Isopropyl Alcohol | 1,000 | A |
| Manganese | 5,000 | B |
| Methylene chloride | 25 | 8 |
| Methylethyl Ketone | 1,000 | A |
| Methyl tert-butyl ether (MTBE) | 100 | 3 |
| Polychlorinated Biphenyls (PCB) | 1 | A |
| Tetrachloroethylene | .5 | ₿ |
| Toluene | 1,000 | A |
| 1,1,1-Trichloroethane | 200 | E |
| Trichloroethylene | 5 | E |
| Vinyl Chloride | 2 | E |

- A Action level adopted in 1979.
- L Action level established 1980-1990 by Connecticut DHS.
- C Action level adopted from federal EPA standard.

GJD/1km 31601

CONTANINATED WELLS IN CONNECTICUT

Total Number of Wells = 1,368



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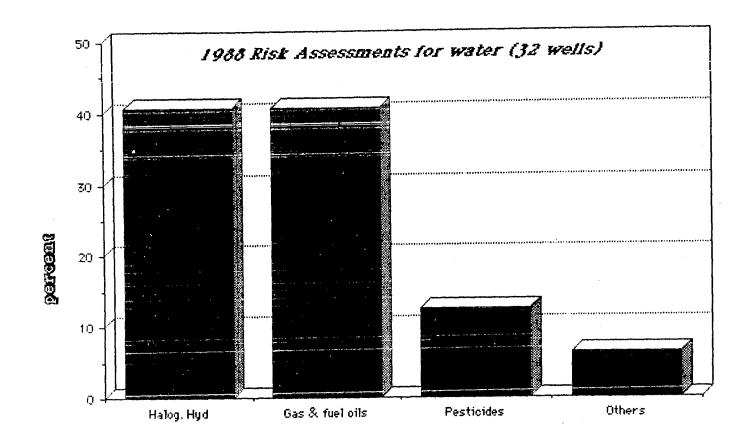
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| | TOTAL NUMBER | ESTIMATED TOTAL | NUMBER OF | ESTIMATED POPULATION |
|-------------|--------------|-----------------|---------------|----------------------|
| CONTAMINANT | OF WELLS | POPULATION | PRIVATE WELLS | FOR PRIVATE WELLS |
| GAS | 202 | 11388 | 118 | 369 |
| FUEL OIL | 59 | 3213 | 55 | 174 |
| SOLVENTS | 406 | 195993 | 241 | 815 |
| EDB | 356 | 37643 | 301 | 1029 |
| PESTICIDE | 69 | 12288 | 65 | 236 |
| Mn | 9 | 29 | 9 | 29 |
| LEACHATE | , i 91 | 671 | 76 | 482 |
| NITRATE | 87 | 327 | 86 | 297 |
| SALT | 110 | 11207 | 80 | 236 |
| OTHER | 35 | 906 | 27 | 133 |

TOTAL NUMBER OF WELLS = 1,368

ESTIMATED TOTAL POPULATION = 255,282

Note: Individual estimated total population includes wells that were counted twice if the



HISTORICAL PERSPECTIVE

CONNECTICUT INVOLVEMENT IN SETTING GUIDELINES/STANDARDS IN DRINKING WATER.

| 1976 | PUBLIC HEALTH CODE ADOPTED EPA ENTERIM PRIMARY AND SECONDARY DRINKING WATER STANDARDS FOR PESTICIDES, RADIONUCLIDES, INSEGNICS AND TOTAL TRIHALOMETHANES |
|------------------------------|--|
| 1979 | CONNECTICUT DES ADOPTED ACTION LEVENS POR 11 VOLATILE CECANICS ON RECOMMENDATION OF EPA REGION 1 |
| 19 80-1990 | DHE DEVELOPED ACTION LEVELS FOR SPECIFIC CERNICALS IN RESPONSE TO WILL CONTAMINATION AND DEP REQUESTS |
| 1983 | DHS AND DEP ESTABLISHED JOINT WORKING COMMITTEE TO SET PRIORITIES FOR VOLATILE ORGANIC REGULATION |
| 1984 | DES SET AN EMERGENCY STANDARD, THEN A FINAL STANDARD FOR EDB |
| 1985 | LEGISLATURE PASSED "POTABLE WATER" BILL: |
| | Terus: |
| - | - PROVISION OF POTABLE WATER INDEDICATELY TO RESIDENTS WITH CONTAMINATED WELLS TUROUGH DEP |
| | - DASIS * HEALTH DETERMINATION BY DOS CONCISSIONER |
| 1905 | CONNECTIONT RIGHT STATE BURYET FORMED BASIS OF PRESENTATION AT MA OFFICE OF DRINKING WATER INTRAC MERTING |
| | - CONNECTICUT DES REVIEWED 50 MAP? SPA MALTN APPISONIES THROUGH PSTRAC PROCESS |
| 1988-19 9 0 | CONTRECTICUT CO-CHAIRED PUBLICATION OF PROBLEMS SHOULD OF PROBLEMS. |
| 1989 | BHS INITIATED REGULATORY PROCESS TO ABOUT NOIS FOR BLOOM VOLATILE ORGANIC CHEMICALS AND OTHERS. |

3161Ì

GASOLINE AND PETROLEUM PRODUCTS

BENZENE

MTBE

FUEL OIL

PESTICIDES

DIELDRIN

CHLORDANE

PCB

DICHLOROPROPANE

OTHERS

FREON

SODIUM

HALOGENATED HYDROCARBONS

CHLORIFORM

TRICHLOROETHYLENE

TETRACHLOROETHYLENE

DICHLOROETHYLENE

TRICHLOROETHANE

MAN JEBOR SHABIS

ad Lade

change the advisory," said spokesman Philip Covington.

proved a controversial food safety bill Wednesday intended to keep any pesticide off crops if it poses at least a one-in-a-million risk of causing cancer. The Bush administration wants a clause added to eliminate differing state pesticide laws in effect now. But the U.S. Public Interest Research Group contends doing so would pre-empt states' right to set stricter food safety standards than the federal government.

partment's criminal division, Edward Dennis Jr., is resigning to join a Philadelphia law firm, The Associated Press reported. Dennis, the first black to head the Justice Department's criminal division, will become a senior partner at the Philadelphia firm of Morgan, Lewis and Bockius, the AP reportedly is unrelated to recent turmoil neral Dick Thornburgh. Dennis

EFFECT OF UNCERTAINTY ON THE STARTING ASSUMPTIONS FOR REGULATORY DECISIONS.

SCIENCE:

Assume that something is not true until it has been conclusively demonstrated to be so to a level of statistical certainty, usually a P value of less than 0.05.

When in doubt a request for more data is the correct decision.

PUBLIC HEALTH:

Forced to take action on suggestive but scientifically inconclusive evidence. Lack of data is often a reason to regulate or to warn about a possible risk.

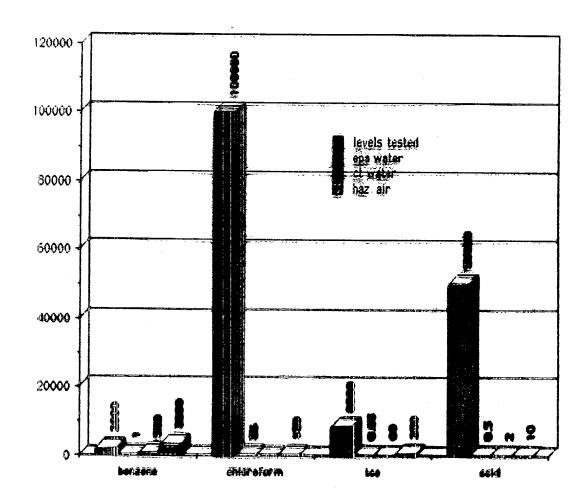
Lack of a decision that continues exposures is considered a decision of absence of risk.

KEY QUESTIONS THAT NEED TO BE ADDRESSED

- 1. Is it likely that a molecular interaction will occur over three orders of magnitude? \mathcal{N}_0
- 2. Is it possible that there are no toxic effects at these exposure levels? N_{\circ}
- 3. Are there any chemicals that are active are the ug/kg levels seen in the environmental studies?
- $4. \ \,$ Are there procedures or techniques more likely to be of value in studies of low level toxicity ?

- 3. Ves TCDA
 Botulism
 lead
 Cobra ven om
 tetanus toxin
 Ricin
- 4. Yes

 Pharmacokinetics
 Inuitro studes
 Studies that monitor



lowest test done vs highest savironmental done (ug/kg)

FACTORS USED TO SET NOELS

- 1. BODY AND ORGAN WEIGHT CHANGES
- 2. TISSUE PATHOLOGY
- 3. HEMATOLOGIC EFFECTS
- 4. MORTALITY
- 5. GROWTH AND DEVELOPMENT
- 6. HEPATOMAS
- 7. TUMORS

LOWEST DOSES REPORTED IN 1988 SOT ABSTRACTS

| COMPOUND | DOSE TO ANIMALS IN EACH REPORT I |
|--------------------|---|
| BENZENE | 2 mg/kg, 25 mg/kg, 200 mg/kg, 586 mg/kg 1 ml/kg, 50-600 ppm, 100-300 ppm |
| CHLOROFORM | 100 mg/kg, 750 mg/kg |
| TRICHLORETHYLENE | 8 mg/kg, 250 mg/kg, 450 mg/kg, 600 mg/kg |
| CARBONTETRACHLORID | E 50 mg/kg, 100 mg/kg, 100 mg/kg |

CONCENTRATIONS AT HAZARDOUS WASTE SITES

| COMPOUND | CONC. IN AIR | DOSE |
|---------------------|--------------|------------|
| BENZENE | 5703 ug/m3 | 3000 ug/kg |
| CHLOROFORM | 266 ug/m3 | 150 ug/kg |
| TRICHLORETHYLENE | 500 ug/m3 | 250 ug/kg |
| CARBONTETRACHLORIDE | 20 ug/m3 | 10 ug/kg |

CONCENTRATIONS OF REGULATED COMPOUNDS IN WATER

| COMPOUND | MAXIMUM CONCENTRATION | ESTIMATED DOSE |
|---|---|--|
| BENZENE | 10 UG/L | 1 UG/KG |
| CHLOROFORM | 366 UG/L | 36 UG/KG |
| TRICHLOROETHYL | ENE 0.5 UG/L | 0.05 UG/KG |
| CARBON TETRACH | LORIDE 5 UG/L | 0.5 UG/KG |
| CHLORDANE | 0.1 UG/L | 0.01 UG/KG |
| ALACHLOR | 2.9 UG/L | 0.3 UG/KG |
| TRICHLOROETHYL CARBON TETRACH CHLORDANE | ENE 0.5 UG/L LORIDE 5 UG/L 0.1 UG/L | 0.05 UG/KG 0.5 UG/KG 0.01 UG/KG 0.3 UG/KG |

Adapted from EPA's Drinking Water and Health

MAXIMUM CONCENTRATIONS OF CHEMICALS REPORTED TO CONNECTICUT DEPARTMENT OF HEALTH SERVICES 1988 AND 1987

| COMPOUND | CONCENTRATION | N | DOSE |
|----------|--------------------|----|---------------|
| BENZENE | 500 860 970 | 14 | 250-500 UG/KG |
| TCE | 12 20 125 | 9 | 6-60 UG/KG |
| TOLUENE | 350 400 460 | 6 | 175-230 UG/KG |
| CCL4 | 3 4 | 2 | 2 UG/KG |
| MITBE | 170 210 3200 | 6 | 65-1600 UG/KG |
| EDC | 2 6.2 12 | 6 | 1-6 UG/KG |

Three highest readings.

The law of mass action suggests that extrapolation of a mechanistic interaction is limited to one or two orders of magnitude.

Question 2 No!

Reports from the public who experience these exposures reveal that there are complaints and that the complaints are relatively similar from episode to episode. It is unlikely that these are not exposure related in some part.

Question 3 Yes!

If one looks in the literature for compounds which are active at the ug/kg levels a large number are found.

eg. TCDD

Botulism toxin

lead

Cobra venom

tetanus toxin

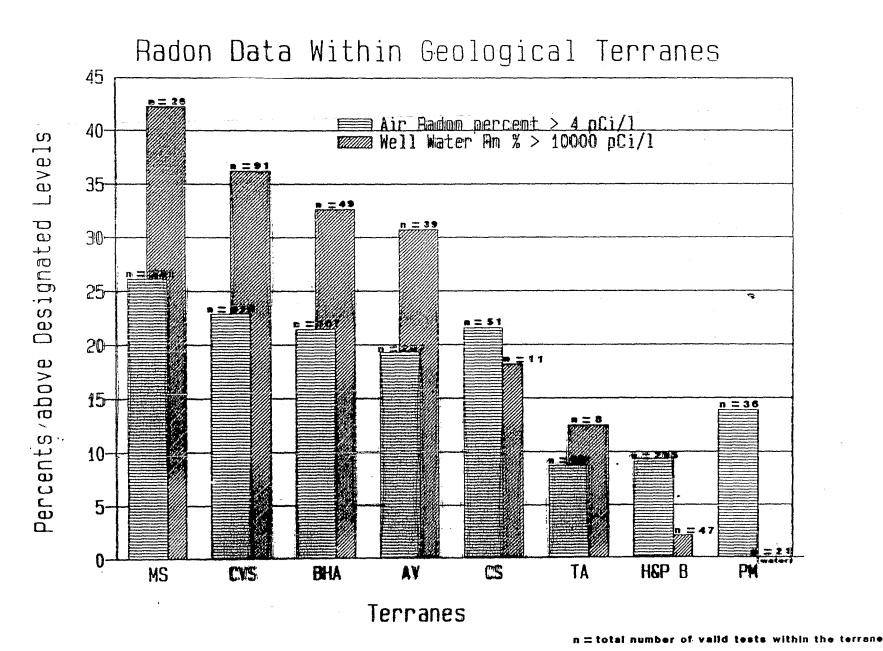
Ricin

A variety of immune responses

Question 4 yes!

Some procedure that seem to be showing great promise are the following.

Pharmacokinetic analysis
Invitro studies
Studies that monitor the condition of the receptor response
Studies that evaluate the immune system
Studies that look a mechanisms for enhancing distribution of active moiety such as glutathione conjugation and break down



SUMMARY OF RADON TEST RESULTS OF THE HOUSEHOLD TESTING PROGRAM (*)

Second Phase Cities and Towns (**) (Testing Conducted February - April, 1988) July 1988

Lowest Livable Area (1.e., basement)

Lowest Lived-in Area (i.e., first floor)

| | | | | | | | | | | • | | |
|---------------|--------|------|-------|-----------|-------|-----------|--------|------|----------------------------|----------|-----------|--------|
| | A | | (pCi, | | # of | | 1 | | (pCi/1 | | | Homes |
| | _ : | | | Geometric | > 4 | > 20 | | | | eometric | > 4 | > 20 |
| | #Tests | Min. | Max. | Mean*** | pCI/1 | pCi/1 | #Tests | Min. | $\frac{\text{Max}}{\cdot}$ | Mean*** | pC1/1 | pCi/1 |
| Andover | 83 | 0.2 | 19.0 | 1.7 | 20% | 0% | 89 | 0.0 | 15.0 | 1.1 | 11% | 0% |
| Branford | 96 | 0.0 | 85.0 | 2.3 | 39% | 1.2% | 97 | 0.0 | 32.0 | 1.1 | 17% | 5% |
| Bridgeport | 78 | 0.1 | 26.0 | 2.2 | 27% | 1% | 79 | 0.0 | 11.0 | 0.9 | 4% | 0% |
| Burlington | 83 | 0.7 | 21.0 | 1.9 | 11% | 1% | 91 | 0.0 | 14.0 | 1.3 | 6% | 0% |
| Chaplin | 86 | 0.2 | 12.0 | 1.8 | 16% | 0% | 85 | 0.1 | 8.2 | 1.3 | 8% | 0% |
| Easton | 92 | 0.2 | 12.0 | 2.5 | 24% | 0% | 96 | 0.0 | 9.1 | 1.5 | 8% | 0% |
| Groton | 96 | 0.0 | 18.0 | 1.8 | 13% | 0% | 99 | 0.0 | 8.0 | 0.9 | 6% | 0% |
| Guilford | 93 | 0.3 | 483.0 | 2.4 | 27% | 5% | 93 | 0.2 | 112.0 | 1.7 | 18% | 1% |
| Haddam | 96 | 0.2 | 47.0 | 3.2 | 38% | 1% | 98 | 0.5 | 43.0 | 2.2 | 22% | 1% |
| Kent | 62 | 0.2 | 17.0 | 2.4 | 29% | 0% | 62 | 0.1 | 9.6 | 1.1 | 13% | 0% |
| M_ldletown | 92 | 0.2 | 21.0 | 1.1 | 11% | 1% | 91 | 0.1 | 21.0 | 0.6 | 6% | 1% |
| Monroe | 91 | 0.2 | 21.0 | 1.4 | 9% | 1% | 91 | 0.2 | 7.3 | 0.8 | 3% | 0% |
| New Hartford | 84 | 0.2 | 11.0 | 1.3 | 11% | 0% | 85 | 0.2 | 21.0 | 1.1 | 8% | 1% |
| N. Stonington | 97 | 0.1 | 45.0 | 1.8 | 27% | 2% | 98 | 0.0 | 39.0 | 1.2 | 12% | 1% |
| Preston | 95 | 0.0 | 12.0 | 1.4 | 12% | 0% | 96 | 0.0 | 7.6 | 0.7 | 3% | 0% |
| Ridgefield | 87 | 0.3 | 19.0 | 1.6 | 9% | 0% | 89 | 0.1 | .11.0 | 0.9 | 5% | 0% |
| Scotland | 19 | 0.3 | 19.0 | 2.1 | 42% | 0% | 20 | 0.2 | 9.8 | 1.0 | 5% | 0% |
| Stonington | 98 | 0.2 | 29.0 | 1.7 | 14% | 2% | 98 | 0.1 | 16.0 | 1.1 | 9% | 0% |
| Voluntown | 78 | 0.2 | 72.0 | 2.4 | 29% | 4% | 79 | 0.0 | 32.0 | 1.9 | 20% | 4% |
| Waterford | 98 - | 0.0 | 8.4 | 1.4 | 5% | 0% | 99 | 0.1 | 6.6 | 1.0 | 6% | 0% |
| √atertown | 84 | 0.3 | 10.0 | 1.8 | 11% | 0% | 88 | 0.3 | 4.6 | 1.2 | 3% | 0% |
| WIndham | 99 | 0.2 | 14.0 | 1.9 | 17% | 0% | 73 | 0.3 | 26.0 | 1.4 | 8% | 1% |
| Woodbridge | 97 | 0.4 | 32.0 | 2.8 | 35% | 2% | 98 | 0.3 | 32.0 | 1.7 | 11% | 1% |
| Woodbury | 94 | 0.3 | 33.0 | 2.5 | 31% | 4% | 94 | 0.2 | 25.0 | 1.7 | 20% | 2% |
| Overall | 2066 | 0.0 | 483.0 | 1.9 | 20% | 2% | 2096 | 0.0 | 112.0 | 1.2 | 10% | 1% |

^{* 48-}hour samples using charcoal devices.

Town

^{**} Sampling emphasized higher radon potential areas, thus overall state radon level is expected to be lower.

*** Because radon data are log-normally distributed, the appropriate descriptive statistic for the average is the geometric mean.



STATE OF CONNECTICUT

DEPARTMENT OF HEALTH SERVICES PREVENTABLE DISEASES DIVISION

SUMMARY OF RADON TEST RESULTS OF THE HOUSEHOLD TESTING PROGRAM (*)

Overall Results for First & Second Phase Municipalities (**) July 1988

Lowest Livable Area (i.e., basement)

Lowest Lived-in Area (i.e., first floor)

| | (pCi/ | | (pCi/1) # of Homes | | | lomes | | | (pCi | i/1) / of | | Homes | |
|-------|--------|------|--------------------|----------------------|--------------|--------------|----------------|-------------|-------|-------------------|--------------|---------------|--|
| | #Tests | Min. | Max. | Geometric Mean*** | > 4 pCi/1 | >20 pCi/1 | # <u>Tests</u> | Min. | Max. | Geometric Mean*** | > 4 pC1/1 | > 20 pCi/1 | |
| TOTAL | 3378 | 0.0 | 483.0 | 2.1 | 21% | 2% | 3409 | 0.0 | 112.0 | 1.3 | 10% | 0.6% | |

First Phase Towns (**)

(Testing Conducted December, 1987 - February, 1988)
Updated Results - June 1988

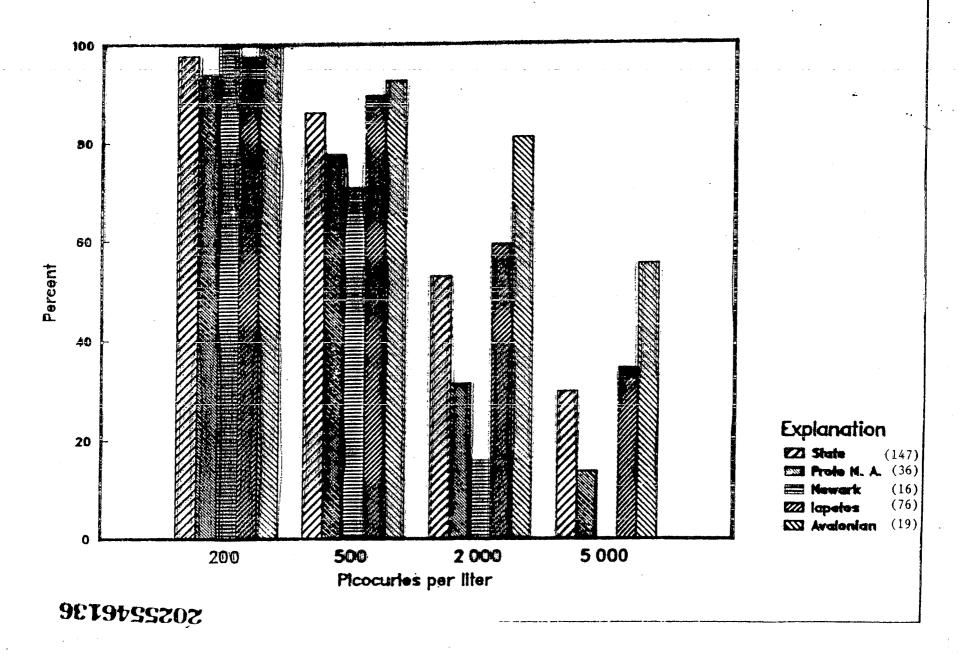
Town

Lowest Livable Area (i.e., basement)

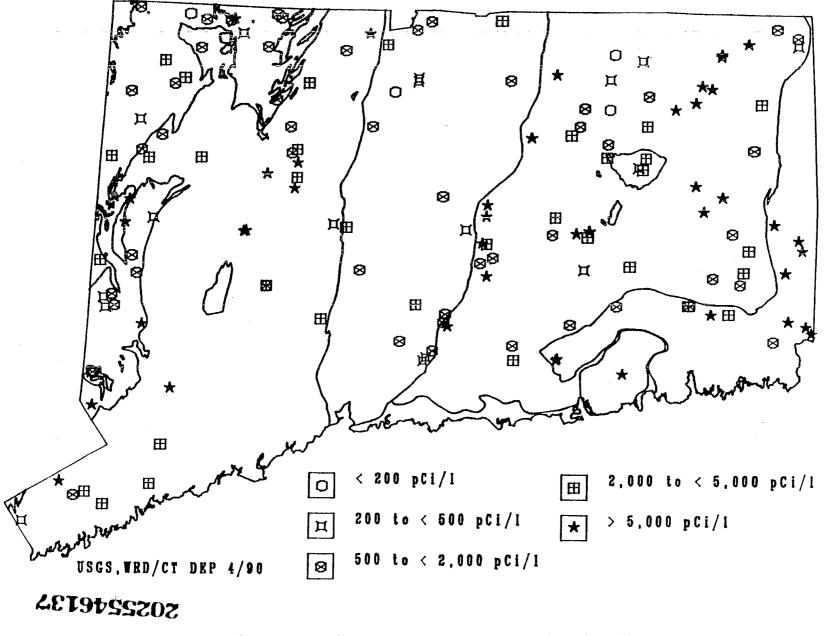
Lowest Lived-in Area (i.e., first floor)

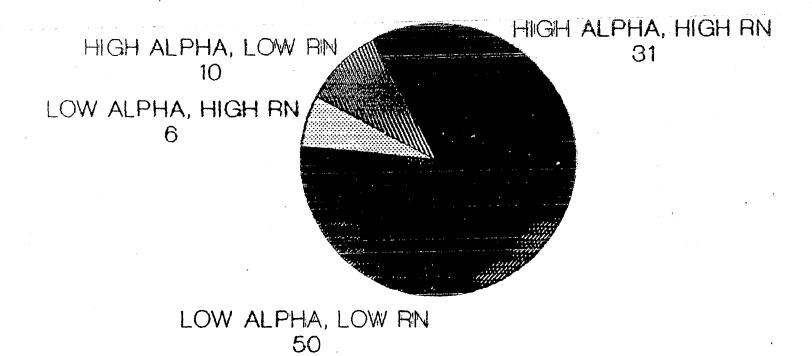
| | | | (pC1/ | 1) | # of Homes | | | (pCi/1) | | | # of Homes | |
|--------------|------------|------------------|-------------------|-----------|------------|-------|--------|---------|-------------------|-----------|------------|------|
| | | | | Geometric | > 4 | > 20 | | | . (| Geometric | > 4 | > 2 |
| | #Tests | Min. | Max. | Mean*** | pCi/1 | pCi/1 | #Tests | Min. | Max. | Mean*** | pCi/1 | pCi/ |
| Ansonia | 93 | $\overline{0.5}$ | $5\overline{8.0}$ | 3.9 | 43% | 9% | 95 | 0.3 | $\overline{19.5}$ | 1.7 | 14% | 0% |
| Bethlehem | 89 | 0.3 | 22.7 | 2.2 | 26% | 1% | 89 | 0.3 | 9.0 | 1.6 | 10% | 0% |
| East Hampton | 91 | 0.4 | 19.1 | 2.5 | 23% | 0% | 91 | 0.3 | 13.6 | 1.6 | 6% | 0% |
| Glastonbury | 103 . | 0.5 | 37.0 | 2.1 | 23% | 4% | 103 | 0.0 | 17.3 | 1.1 | 11% | 0% |
| Goshen | 91 | 0.1 | 75.0 | 2.1 | 22% | 2% | 91 | 0.2 | 25.5 | ,1.5 | 11% | 1% |
| Madison | 9 9 | 0.3 | 36.3 | 3.2 | 37% | 5% | 99 | 0.2 | 34.7 | 1.5 | 14% | 1% |
| Mansfield | 93 | 0.6 | 10.0 | 2.2 | 10% | 0% | 94 | 0.5 | 4.9 | 1.6 | 3% | 0% |
| Montville | . 99 | 0.7 | 25.3 | 2.4 | 15% | 1% | 98 | 0.7. | 10.4 | 1.9 | 10% | 0% |
| Pomfret | 81 | 0.8 | 13.8 | 2.2 | 6% | 0% | 81 | 0.7 | 7.3 | 1.7 | 3% | 0% |
| Portland | 97 | 0.4 | 30.4 | 1.7 | 13% | 2% | 97 | 0.4 | 12.7 | 1.2 | 3% | 0% |
| Torrington | 93 | 0.8 | 37.8 | 2.2 | 18% | 1% | 93 | 0.5 | 10.7 | 1.4 | 10% | 0% |
| Trumbull | 88 | 0.8 | 15.2 | 2.5 | 16% | 0% | 88 | 0.5 | 12.8 | 1.5 | 6% | 0% |
| Weston | 96 | 0.9 | 98.4 | 3.3 | 35% | 4% | 97 | 0.8 | 35.2 | 2.3 | 19% | 1% |
| Westport | 97 | 0.6 | 49.0 | 3.1 | 30% | 3% | 96 | 0.6 | 36.5 | 2.0 | 16% | 2% |
| Overal: | 1312 | 0.1 | 98.4 | 2.5 | 23% | 2% | 1313 | 0.0 | 36.5 | 1.6 | 10% | 0.4~ |

S025546135



CONNECTICUT BEDROCK WELL WATER RADON





Discussion Session--Risk Analysis for Specific Contaminants

ALAR (Daminozide)

Graham

INTRODUCTION TO DISCUSSION SESSIONS

I. ALAR (Daminozide)

ALAR is a hydrazine compound that has been used as a plant growth regulator since 1962. The EPA established in 1976 residue tolerances of 1 to 55 ppm on a variety of fruit. In 1987, EPA reaffirmed a limit of 20 ppm for apples.

This compound was selected for discussion because:

- 1. It is typical of cases that appear to have confronted regulators without warning.
- 2. Data on its health effects are sparse and only exist for exposures to animals.
- 3. The public (stimulated by the Natural Resources Defense Council) demanded prompt action.
- 4. Other hydrazine compounds have been found to be carcinogenic.

In its challenge, the NRDC claimed that chemical residues of ALAR, especially on apples, were causing elevated risks of cancer among children. To emphasize their point, NRDC held news conferences in a dozen cities and warned that over 5,000 children might die from preschool exposures to ALAR. Ed Bradley (on "60 Minutes") stated that ALAR was "the most potent cancer-causing agent in our food supply."

As a result, apples disappeared from many grocery shelves and cafeteria lines. Meryl Streep appeared on "Donahue" and the "Today" Show announcing formation of "Mothers and Others for Pesticide Limits." Because of these actions, the apple industry suffered an estimated \$100 million loss; some growers were actually forced out of business. Other impacts included the introduction of a bill in the Senate to ban the use of ALAR. And the media praised NRDC for its humanitarian efforts.

On the basis of subsequent thorough reviews of the literature and scientific data, these charges were largely refuted. In fact, the National Academy of Sciences (NAS) publication, <u>Issues in Science and Technology</u>, stated that

ALAR poses no health threat. The NAS report, which was based on an examination of 6,000 studies, found "no evidence that pesticides or natural toxins in food contribute significantly to cancer risk in the United States."

To provide background for a review of this case, you have been provided with selected reports and publications on ALAR. These include a copy of the NRDC report. Questions that you may want to consider in evaluating this issue include:

- 1. Statistical analyses of the data seem to show an excess of tumors in animals exposed to ALAR. (See paper by Gold, et al.). In light of this, why did EPA reviewers not agree?
- 2. Is it fair to use data at the 80 ppm level as evidence for the carcinogenicity of UDMH, a metabolite of ALAR?
- 3. If ALAR and UDMH are assumed to be carcinogenic, what are their potencies?

Dr. John Graham will be discussing these and related issues on Friday morning at 9:45.

II. Dioxin

Dioxin is a byproduct of the manufacture of herbicides. It was first detected in the late 1950s when it was observed as a contaminant that forms during the commercial synthesis of 2,4,5-trichlorophenoxyacetic acid, a compound used as a weed killer and in Agent Orange.

Animal studies have shown that this ubiquitous pollutant is extremely lethal; in fact, it is the most potent carcinogen ever tested. But human effects have been notoriously difficult to confirm -- as exemplified by the decades old controversy over the effects of Agent Orange.

This is an interesting issue to review for several reasons:

- 1. The highly controversial nature of the effects of this compound.
- 2. The accusations that industrial groups withheld information that was important to evaluations of its health effects.
- 3. The success of bringing disparate groups together to discuss and reach a consensus on the related health effects issues.

4. The far-reaching implications of the consensus reached in this particular case.

In the absence of definitive human data, the EPA assumed that there is no safe level for dioxin, that is, that the dose - effect relationship was linear. Following this approach, EPA set an acceptable intake level of 0.006 picograms per kilogram of body weight per day. Following a non-linear approach, Canada and several of the European countries set limits that were 170 to 1700 times higher than that recommended by EPA.

At a meeting at the Banbury Center at the Cold Spring Harbor Laboratory, 38 researchers and regulators from the U.S. and Europe recently reached agreement on the health effects of dioxin. Specifically, they agreed that, before dioxin can cause its myriad toxic effects, be they cancer or birth defects, it must first bind to and activate a receptor.

The importance of this agreement is that, if receptor binding is an essential first step before any toxic effects can occur, then that implies that there is a "safe" dose or practical "threshold" below which no toxic effects occur. This also indicates that the linear non-threshold model does not apply. An additional implication of the acceptance of this approach is that there could be significant changes in current assessments of the risks of many other chemical compounds in common use today.

You have been provided with several background papers on this subject. Dr. Linda Birnbaum will be here on Friday morning at 11:15 to discuss this issue in greater detail. Questions that you may want to consider in discussing this topic include:

- 1. How valid is the assumption that the necessity for receptor binding assures that a chemical compound has a threshold for toxic effects?
- 2. If there is a threshold for dioxin, what is it? Are there sufficient data available to determine whether dioxin intake of the U.S. population is below this threshold?
- 3. How many other toxic compounds must first bind to an activate a receptor? That is, how far reaching are the implications of the findings with respect to dioxin?

III. Lead

Lead is of concern both in the occupational and ambient environment. Major sources of intake for the general public include the ingestion of lead from drinking water that has either flowed through lead pipe or pipe in which lead was used as a solder; eating from lead glazed dishes; consuming vegetables grown in lead contaminated soil; and eating food that has been contaminated by lead that has leached from crystal and plastic food bags. A major source of lead among children is through the consumption of lead-based paint in houses. Although it has been illegal for more than 50 years to use lead paint in houses, it is estimated that over 40 million homes in the U.S. still contain hazardous quantities of leaded paint.

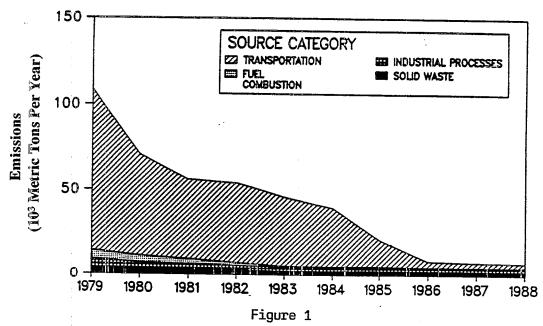
A second major source of lead intake by the general public is through inhalation of lead oxide from automobile exhausts and from suspended soil dust. Of the lead in gasoline, approximately 75% is released with the exhaust gases. Of this, about 35% is emitted as a submicrometer-sized aerosol; about 40% is emitted as >10 micrometer sized particles. In 1970, about 190,000 metric tons of lead were released into the atmosphere in the U.S. through the combustion of gasoline. Through prohibition of the use of lead in gasoline, this had been reduced to about 100,000 metric tons in 1979. Today, releases from this source amount to less than 5,000 metric tons (Figure 1).

Lead is considered to be an interesting issue to review for several reasons:

- 1. There is a multitude of sources through which the population can be exposed. As a result, assessment of <u>exposures</u> is difficult; measurements of <u>doses</u>, whenever practical, is clearly a superior method for estimating potential health effects.
- 2. Lead appears to have a range of health effects; these include neurobehavioral effects in children and blood pressure effects in adults. No single mechanism appears sufficient to account for these effects.
- 3. Conventional animal toxicological studies of lead appear to provide little information about serious human chronic health issues.

You have been provided with a selection of background reports on this topic. Dr. Howard Hu will be here Friday afternoon at 1:15 to discuss this subject in detail. Questions that you may want to consider include:

- 1. Are there good methods for estimating doses occurring as a result of exposures to lead? In this regard, how useful are measurements of lead levels in blood or in urine?
- 2. Since each health effect thought to result from exposures to lead may have a different causitive mechanism, might there be a different relation between dose and effect for each? What is the likelihood that any of the observed health effects from lead will show a linear non-threshold relationship to dose?
- 3. Whereas lead acetate has been shown to be carcinogenic in animals, this is not the chemical form to which humans are commonly exposed. The carcinogenicity of organic compounds is dependent on the specific chemical compound. Should the same be assumed for lead?
- 4. Two of the health effects of lead are thought to be a reduction in IQ and an increase in blood pressure. In this regard, what are the public health implications of a 4 point reduction in IQ or a 3 point increase in blood pressure?



Airborne Emissions of Lead in the United States -- 1979 - 1988

Risk Assessment in Environmental and Occupational Health

School of Public Health Harvard University

Risk of ALAR (daminozide) Prepared by Susan Moses and Richard Wilson

DATA:

Chemical name DAMINOZIDE (CAS 1596-84-5)

IT is a hydrazine compound that has been used as a plant growth regulator since 1962.

The Environmental Protection Agency (EPA) in 1976 established residue tolerances of 1-55 ppm on variety of fruits that include cherries, plums, apples, nectarines, peaches, pears, grapes, melons, tomatoes, brussel sprouts, peppers and peanuts. Residues of 0.02 - 2ppm are allowed in meat or milk. In 1987 they reaffirmed a limit of 20 ppm on apples.

we selected this as a case study for a number of reasons.

- 1) It is typical of cases which hit regulators and others out of the blue.
- 2) Data is sparse and only exists for exposures to animals in rodent bioassays.
- 3) Immediate action was demanded by a segment of the public.
- 4) Other hydrazine compounds have been shown to be carcinogenic.

The principal use of ALAR on apples is often regarded as a "non-essential" use, although such phrases depend very much on the individual. Its purpose is to make the apple redder and more attractive: It is also used to control the shelf life of the apple and the market quality at harvest.

ANIMAL BEOASSAY ON DAMINOZIDE:

Daminozide has been treated in a whole life bioassay by the NCI/NTP (National Toxicology Program). It is covered in Technical Report #83 published in 1977.

The reviewers for these data concluded that "under the conditions of these bioassay, daminozide was not carcinogenic in the Fischer 344 rats or in the female B6C3F1 mice. In male B6C3F1 mice, the induction of hepatocellar carcinomas may have been associated with the administration of the test chemical. Daminozide was carcinogenic in female Fischer 344 rats, inducing adenocarcinoma of the endomentrium of the uterus and leiomyosarcomas of the uterus". However, the EPA

decided, on recommendation of their Science Advisory Board, that this was insufficient evidence of carcinogenicity.

Attached (attachment 1) are computer generated plots and significance data from the NCI/NTP data using a program called MSTAGE written by Dr. Crouch.

- 1. interstitial liver tumors in testis of male rat.
- 2. lung tumors in female rats.
- 3. liver tumors in male mice.
- 4. tumors of uterus in female rats.
- 5. lung tumors of male mice.

Gold et al in their Carcinogenic Bioassay Data Base (et al includes Bruce Ames) have calculated for Daminozide (Environmental Health Perspectives <u>58</u>, page 86, 1984).

a "TD50" of

- 2.15 gms/kg liver tumors ins male mice
- 1.24 gms/kg total tumors in male mice
- 0.88 gms/kg tumors in male mice
- 4.89 gms/kg lung tumors in female rats

This is the dose at which 1/2 the animals could get cancer.

THE METABOLITE UDMH:

In addition we note that there is a metabolite of Daminozide called UDMH. This is produced by Daminozide in the body of the rodents and probably also in people, and may be the active toxic agent, or cancer causing agent (if it causes cancer). Moreover, UDMH is also present, to a few percent, in the apples. (This is the only pesticide where an active metabolite is found in large quantity with the pesticide).

There is no NCI/NTP study on UDMH, but there is a recently concluded study by International Research and Development Co. The results (pp 47 and 48) are attached. There is an increase in lung adenomas at the high dose group as noted on p. 9 of "Summary of Toxicological data on Daminozide and UDMH".

DOSE:

To estimate to people, we need to know exposure.

What was the concentration in apples? How many apples do people eat?

NRC and EPA in the attached documents make different assumptions.

QUESTIONS

During the next two days the participants should ask the following questions:

- 1) A simple application of statistical analysis to the data seems to show a statistically significant excess of tumors in animals exposed to DAMINOZIDE. This can be seen in the data as plotted. Gold et al, using a different statistical technique agree. Why did the EPA reviewers of the NCI document #83 not seem to agree? What do you think?
- 2) Is it fair to use the data at the 80ppm dose as evidence for carcinogenicity of UDMH?
- 3) $\underline{\text{IF}}$ Daminozide and UDMH are assumed to be carcinogenic, what are their potencies ?
- 4) Which are the reasonable dose scenarios NRDC or EPA or neither?
- 5) What is the calculated risk on these assumptions?

At the end of the course, Dr. Graham will discuss some management questions with you (refer to attached case).

Attachments

- 1. Graphs of data from NCI/NTP 83 "DAMINOZIDE"
- 2. pp. 47 & 48 from IRDC study on UDMH
- 3. "Intolerable Risk: Pesticides in our children's food: NRDC Feb. 27, 1989.
- 4. "Daminozide: a special review" EPA, May 1989.
- 5. Summary of Toxicology data on Daminozide and UDMH (Uniroyal).
- 6. Letter to Science by Bruce Ames and Lois Gold.

Intolerable Risk: Pesticides in our Children's Food

A Report by the Natural Resources Defense Council

February 27, 1989

2025546150

Executive Summary

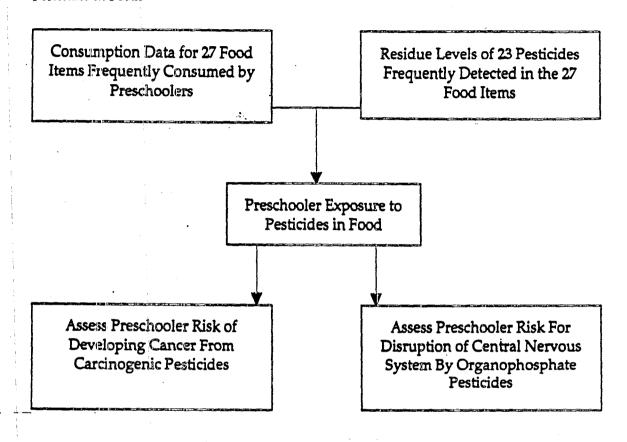
Our nation's children are being harmed by the very fruits and vegetables we tell them will make them grow up healthy and strong. These staples of children's diets routinely, and lawfully, contain dangerous amounts of pesticides, which pose an increased risk of cancer, neurobehavioral damage, and other health problems. Although solutions are at hand, little is being done by the government to protect children from the intolerable risk to their health posed by pesticide residues in food.

In 1986, the Natural Resources Defense Council (NRDC) began a major study to determine whether levels of pesticide residues currently found in fruits and vegetables pose a health hazard to preschoolers. The potential effects of pesticide residues on children were examined for several reasons. First, the typical child consumes fruits and vegetables at a significantly greater rate than adults. With this increased intake comes greater relative exposure to pesticides present in food. Second, children may be more vulnerable to the effects of toxic chemicals, including pesticides. Experimental studies have found that the young are frequently more susceptible than adults to carcinogens and neurotoxins. Finally, although the Environmental Protection Agency (EPA) acknowledged in 1987 that children are invariably exposed to the highest levels of pesticides in food, neither the preschooler's dietary exposure to pesticides nor the resultant health risk has been previously quantified in a comprehensive manner. NRDC's report, therefore, represents the first detailed analysis of children's exposure to pesticides in food and a determination of the potential hazard that these residues pose to children.

Methodology

NRDC estimated the health risk to preschoolers during their first six years of life (0-5 years) by determining consumption rates for food items most frequently eaten by children. Data on the quantities of 23 pesticides known to have adverse health effects and commonly detected in these foods were obtained from federal government regulatory programs. Preschoolers' exposure to these 23 pesticides was determined by combining children's consumption rates for the food types with actual pesticide residue levels found in these foods. Pesticide exposure estimates were then assessed to determine preschoolers' risk of developing cancer or experiencing a disruption in central nervous system function. These toxicological endpoints were selected because 20 of the 23 pesticides evaluated in this report are either neurotoxic or carcinogenic. Furthermore, risk assessment procedures for these health effects are fairly well established. Figure S-1 provides a schematic representation of the methodology

Figure S-1. Methodology of NRDC Study to Estimate Preschoolers' Health Risk From Pesticides in Foods



To develop an adequate database of preschooler exposure to pesticides, NRDC used consumption data from a nationwide food consumption survey conducted in 1985 by the U.S. Department of Agriculture (USDA) of children and adult women, and data on residue levels of 23 pesticides (and important metabolites) actually measured in types of fruits and vegetables. The data on pesticide residues in produce were derived from analyses of over 12,000 food samples conducted under regulatory programs of the Food and Drug Administration (FDA) and the EPA.

Principal Findings

Preschoolers are being exposed to hazardous levels of pesticides in fruits and vegetables. Between 5,500 and 6,200 (a risk range of 2.5 x 10⁻⁴ to 2.8 x 10⁻⁴) of the current population of American preschoolers may eventually get cancer solely as a result of their exposure before six years of age to eight pesticides or metabolites commonly found in fruits and vegetables. These estimates are based on scientifically conservative risk assessment procedures. They indicate that more than 50% of a person's lifetime cancer risk from exposure to carcinogenic pesticides

used on fruit is typically incurred in the first six years of life.

The potent carcinogen, unsymmetrical dimethylhydrazine (UDMH), a breakdown product of the pesticide daminozide, is the greatest source of the cancer risk identified by NRDC. The average preschooler's UDMH exposure during the first six years of life alone is estimated to result in a cancer risk of approximately one case for every 4,200 preschoolers exposed. This risk is 240 times greater than the cancer risk considered acceptable by EPA following a full lifetime of exposure. For children who are heavy consumers of the foods that may contain UDMH residues, NRDC predicts one additional cancer case for approximately every 1,100 children, a risk 910 times greater than EPA's acceptable level.

The carcinogenic risk estimates for daminozide are based on results of a 1986 market basket survey that EPA required the manufacturers of daminozide to conduct. Although daminozide use may have decreased since 1986, there is no reliable in-_formation on whether—or to what degree use has decreased. EPA has recently stated that approximately 5% of apples are treated with daminozide. However, this figure was derived from informal conversations with growers, who may have a strong self-interest in portraying their products as daminozide-free. In contrast to EPA's figure, one Uniroyal manager privately stated that 10-11% of the nation's apple acreage was treated with daminozide in 1988. Further, an independent laboratory found in 1988 that 30% of apples tested from one large supermarket chain contained daminozide. More recently, a survey indicated that 23% of Vermont's apple acreage was treated with daminozide. These data were not considered when EPA developed its use estimate and raise serious questions about the accuracy of the Agency's figure. In the absence of government testing to verify grower claims about daminozide use, the manufacturer's 1986 market basket survey remains the only accurate indicator of actual residues in food.

Preschoolers also receive unacceptable exposure to the carcinogenic fungicides capchlorothalonil, folpet, ethylenethiourea (ETU), the metabolite of the fungicide mancozeb. NRDC estimates that average exposure to these pesticides from consumption of fruits and vegetables from birth through age five may present a lifetime risk of one cancer case for every 33,000 to 160,000 children exposed. That means that out of the current preschool population, between 140 to 670 children may develop cancer sometime during their lifetime as a result of exposure to these fungicides. These risk estimates are approximately two to seven times what EPA considers acceptable following a full lifetime of exposure. These estimates are unchanged by EPA's recent decision to cancel certain food uses of captan since none of the food uses contributing to preschoolers' risk in our calculation were cancelled by EPA.

Of equal concern is NRDC's estimate that at least 17% of the preschool population, or three million children, receive exposure to neurotoxic organophosphate insecticides just from raw fruits and vegetables that are above levels the federal government considers safe. High level exposure to these insecticides can cause nausea, convulsions, coma and even death. Dietary exposure received by preschoolers may induce behavioral impairments and alter neurological function.

NRDC's analysis of exposure, based on studies of food consumption by children and women, determined that, relative to their weight, preschoolers receive much greater exposure than adults to the majority of the pesticides analyzed in this report. The A average preschooler receives more than five times greater exposure to the fungicide mancozeb, nine times greater exposure to the neurotoxic organophosphate azinphosmethyl and 12 times greater exposure to UDMH, the carcinogenic metabolite of daminozide, than adults. The typical preschooler receives four times greater exposure, on average, than adults to the eight carcinogenic pesticides evaluated. The youngest children receive the greatest pesticide exposure. Relative to adult women, toddlers receive more than eight times the exposure to mancozeb, 15 times greater exposure to azinphosmethyl and 18 times greater exposure to UDMH.

Preschoolers have greater exposure to pesticide residues than adults because they eat more food, relative to their weight, and consume much larger quantities of fruit, which have a high likelihood of being contaminated with pesticides. Fruit comprises 20% of the adult diet and 34% of the preschooler's diet. Preschoolers eat six times as much total fruit, seven times more grape products and seven times more apples and apple sauce, relative to their weight, than adults. Apple juice is a particular favorite of children. The typical preschool child consumes almost 18 times as much apple juice and the typical toddler more than 31 times as much apple juice, relative to his/her weight, than the average adult woman.

Fruit is highly likely to contain pesticide residues. The 1987 FDA's food monitoring program found that 50% of all fruit samples had detectable levels of pesticides. This contamination rate is higher than that of any other commodity and may significantly underestimate the full extent of contamination. Routine FDA monitoring methods cannot detect approximately 60% of the pesticides likely to leave residues on food, including many carcinogenic fungicides used widely on fruit.

Report Findings May Underestimate Preschooler Risk

The NRDC study may significantly underestimate the full extent of preschooler exposure and the subsequent health risk from pesticides in food for several reasons. First, this study assesses cancer risk that results from exposure only from birth through age five to pesticides in food. The total lifetime cancer risk will be greater since estimates do not include risk incurred from age six to 70+ years. Further, this study assesses the health risk from only 23 pesticides out of the 300 that can be legally used on food. Of the 66 pesticides EPA believes to be potentially carcinogenic and allows to be used on food, only eight were evaluated by NRDC. Routinely used FDA monitoring methods from which much of the residue data used in the NRDC analysis were obtained—can detect only approximately 40% of the pesticides likely to leave residues on foods. Of all food use pesticides classified by the federal government as posing a moderate to high health hazard approximately 40% cannot be detected by FDA monitoring techniques.

NRDC has only assessed exposure from fruits and vegetables out of the many commodities that are consumed daily by preschoolers and that may contain pesticide residues. Milk products are perhaps the most conspicuous of the foods absent from the exposure estimates. The average preschooler has a milk intake that is almost five times higher than that of the typical woman. EPA estimates that 60% or more of the preschooler's exposure to the carcinogenic fungicide captan, for example, may come from residues in milk. EPA's recent cancellation of the minor food uses of captan does not appear to reduce this estimated exposure from milk. Pesticides get into animal products, including meat and eggs, as well as milk, via

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pesticide-contaminated feed. Drinking water may also be a significant source of pesticide exposure, especially in rural areas. EPA has reported that the normal agricultural use of pesticides has resulted in detectable concentrations of 46 pesticides in the groundwater of 26 states.

This report focuses primarily on the risk of developing cancer or the probability of disruption of normal nervous system function from dietary exposure to pesticides. However, many of the pesticides in the study cause additional adverse health effects, such as damage to the kidney or liver, effects on the immune system, or changes in reproductive capacity. Further, the full impact on preschooler health from exposure to pesticides in food is unknown since the majority of the 600 active pesticide ingredients (representing 50,000 pesticide products actually in use) have not been tested according to modern testing requirements, or the test data are unacceptable by today's standards. The National Academy of Sciences (NAS) concluded in 1984, based on an analysis of a representative sample of pesticides, that data needed to conduct a complete health hazard assessment were available for only 10% of the pesticide products on the market. Of the 23 pesticides evaluated for NRDC's study, 19 (83%) were registered by USDA in the 1950s and 1960s before any comprehensive testing requirements were in place. EPA simply adopted their registrations later.

This study underestimates the risks to children for a number of other important reasons. Children are likely to be more susceptible to the effects of nervous-system toxins and cancer-causing chemicals than we have assumed in making our estimates. However, data regarding the degree of enhanced sensitivity in preschoolers were not available for the specific pesticides evaluated in this report; therefore, susceptibility could not be factored into our health risk assessment.

The government does not require adequate testing for neurotoxic effects of pesticides. Long-term neurological testing for chronic effects of organophosphates and other neurotoxic pesticides is not required; the current tests assess only if the pesticide is capable of causing a specific delayed paralytic reaction following acute and subacute exposure.

Finally, "inert" ingredients, which act as the delivery vehicles for the active ingredients, are not regulated, even though many are known to cause cancer or other health hazards. Moreover, EPA has historically not required submission of health or safety information on "inerts". These compounds, labeled "inert" because they have no pest-killing action, have been exempted from federal requirements for setting permissible residue levels for pesticides in food.

Children's Physiological Vulnerability to Toxic Chemicals

Preschool children are receiving hazardous exposures to pesticides at the time when they are likely to be most susceptible to the toxic effects of these compounds. Experimental tests in laboratory animals have found the young to be more vulnerable than adults to the toxic effects of many chemicals, including a number of pesticides, due to their immature physiological systems. Studies have found that the young of various species retain a greater portion of a given dose of certain toxins than adults, because gastrointestinal absorption is increased and elimination is decreased. Further, the young are not capable of detoxifying many chemicals because detoxification enzymes are not fully functional. Young bodies are not capable of segregating toxins from the target organs.

Numerous studies have found that there is a greater risk of developing cancer if exposure to carcinogens begins during infancy rather than later in life. One reason that the young are more susceptible than adults to carcinogens is because cells are dividing rapidly during childhood. The cancer process is typically started when a carcinogen interacts with a cell's DNA, causing a mutation. If cells are dividing rapidly following exposure to a carcinogen capable of mutating DNA, there is a greater probability that the mutation of DNA will be fixed and the carcinogenic event initiated. In addition, the young may be at greater risk of developing cancer because they have a greater probability compared to adults of surviving the latency period prior to the manifestation of cancer

The young have also been shown to be at greater risk from exposure to a number of neurotoxins, including neurotoxic pesticides. For instance, young rats are more susceptible than adults to the acute effects of 15 out of 16 organophosphate pesticides tested. In addition, experimental studies indicate that exposure to organophosphates and carbamate pesticides during the period of nervous system development surrounding birth may alter neurological function and may cause subtle and long-lasting neurobehavioral impairments.

Inadequate Government Programs

Current federal regulation of pesticides fails to protect the preschooler. EPA has virtually ignored infant and child food consumption patterns when regulating pesticides. Current legal limits for pesticides, or tolerances, in food are based on data collected over two decades ago on adult consumption levels. The consumption estimates that have been used by EPA in setting almost all current legal limits for pesticide residues

on produce greatly underestimate preschooler intakes for most produce. Preschooler consumption of cranberries is 14 times greater than EPA's estimates; consumption of grapes is six times greater; apples and oranges, five times greater; apricots, almost four times greater; strawberries, almost three times greater; broccoli, two-anda-half times greater; carrots, two times greater; and tomatoes, one-and-a-half times greater than EPA's estimates.

Because EPA has neglected preschooler consumption rates, the preschooler's maximum legally permissible exposure to many pesticides is hundreds of times higher than the level that EPA considers safe. The average preschooler exposure at legal limits to any one of the carcinogens captan, folpet and mancozeb, would present a risk of approximately one cancer case for every 2,000 to 3,000 children exposed simply during their first six years of life (340-460 times greater than EPA's "safe" standard of one cancer case per million following a full lifetime of exposure). Although EPA recently cancelled several food uses of captan, none of the commodities contributed significantly to actual preschooler exposure to captan. In other words, EPA has permitted the continuation of the captan food uses that present preschoolers with the greatest risk.

Legal exposures to neurotoxic pesticides also pose unacceptable risks. Preschooler exposure at the legal limit to demeton, a neurotoxic pesticide, would exceed the EPA-determined safe level by approximately 400 fold; exposure to another neurotoxin, disulfoton, by approximately 180 fold; and to another, diazinon, by approximately 160 fold.

Recommendations for Reform

Fundamental reforms in federal regulation are necessary if preschoolers are to be adequately protected from pesticides in food. Immediate action is necessary to close the loopholes in EPA's and FDA's regulatory programs. Further, Congress must act to assist growers in reducing their use of pesticides.

Congress must establish health-based standards for pesticide residues in food and require EPA to regulate pesticides so that the most exposed and most vulnerable members of society—infants and children—are adequately protected. EPA's current practice of basing risk assessment on the average diet does not provide this protection. Exposure at the legal maximum, or the tolerance level, should be assumed when EPA conducts risk assessments. EPA must ensure that consumption of food with residues at the legal maximum is safe for everyone, including children.

Congress must clarify EPA's authority to revoke or modify tolerances swiftly when dietary exposures to pesticides are found to present significant risk. It currently takes years to lower tolerances or remove hazardous pesticides from the market. In addition, EPA must consider risks from "inert" ingredients when regulating pesticides. Further, EPA should prohibit the use of dangerous "inerts." Congress should require that pesticide registrants develop practical analytical methods to detect pesticide residues, which can be effectively used by the government in enforcing tolerances. Finally, neurotoxicity testing should be required for all pesticides used on food and should evaluate both acute and long-term adverse effects on such processes as learning ability, memory, intelligence and behavior.

FDA must improve its methods for detecting pesticides in food. Accurate and detailed pesticide use information for both domestic and imported produce must be obtained to facilitate the choice of analytical method used in food samples. To do this, FDA's monitoring resources must be en-

hanced. Congress should require FDA to accelerate its analysis of food samples and give FDA the authority to detain domestic food shipments to insure that food with illegal residues can be removed from the market before it is sold or consumed. In the vast majority of cases, FDA currently fails to take action to prevent illegal food from reaching the market and being sold.

Congress must assist growers in reducing pesticide residues, by providing credit assistance, crop insurance and other financial protection for growers who are changing from conventional, chemical intensive agricultural practices to innovative, lowinput techniques. Congress should impose a tax on pesticide use to fund demonstration of farming techniques that will result in lower pesticide residues. Congress should establish national definitions of "integrated pest management" and "organic" farming techniques and develop a national certification process for commodities grown using these techniques. Congress should modify federal farm support programs to reward growers for using fewer chemicals and ensure that growers are permitted to use crop rotation and other pesticide-reducing techniques without jeopardizing their eligibility for commodity program benefits. Congress should legislatively modify agricultural supply-control systems to ensure that they do not create demand for cosmetically perfect produce which require excessive pesticide use.

Consumer Action

There are measures for limiting an individual's exposure to pesticides in food. However, specific advice is difficult to offer because data on this issue are generally scarce. The steps include: washing all produce, preferably with a diluted solution of dishwashing soap; buying domestically grown produce, preferably in season; pur-

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chasing organically grown fruits and vegetables; and being wary of perfect looking produce since it may contain higher pesticide residues. Ultimately, the best way to minimize the presence of pesticide residues in food is by reducing the widespread use of these chemicals in agriculture. Consumers can accelerate this transition in agriculture through their power in the market place. By demanding food without pesticide residues, consumers will deliver a clear message to our food producers and provide an incentive for farmers to decrease their use of pesticides.

Report Format

The NRDC study is arranged as follows: Chapter One examines food consumption differences between preschool children and adult women and quantifies the preschooler's exposure to 23 pesticides from consumption of different fruits and vegetables. Chapter Two estimates the potential health risk to preschoolers from exposure to these 23 pesticides, with emphasis on cancer risk and nervous system effects. Chapter Three examines the physiological immaturities of the young that make them more susceptible to the toxic effects of chemi-

cals. Chapter Four describes the flaws in the government's regulation of pesticides that permit preschoolers to be exposed to significant health risks. Chapter Five recommends congressional measures necessary to reform these regulatory programs and make the food supply safe from pesticides. Chapter Six offers advice on how to reduce an individual's exposure to pesticide residues. There are three technical appendices. Appendix One contains a detailed description of the methodology used to estimate the preschooler's exposure to the 23 pesticides analyzed. Appendix Two explains the methodology used to conduct the health risk assessments for exposure to organophosphate insecticides. Appendix Three sets forth the methodology used to make the carcinogenic risk assessments.

Ten days prior to publication of this report, EFA cancelled a number of food uses for the pesticide captan. However, the EPA action does not change NRDC's estimates of the carcinogenic risk captan poses to preschoolers presented on pages 3, 37, 38, 39 and 40 of this report. The NRDC estimates are for the lifetime cancer risk that results just from preschooler exposure to dietary residues of captan typically found only in the 27 fruits and vegetables examined in this report. NRDC's risk estimates for cancer are unchanged by EPA's action because none of the food uses contributing to preschooler risk were cancelled by EPA. In fact, EPA has allowed the use of captan to continue on strawberries, apples, grapes, and plums all major dietary sources of preschoolers' exposure to the pesticide.

EPA's action does decrease NRDC's calculation of the preschooler's maximum legally allowed exposure to all uses of captan, and the resulting cancer risk, from 4.6 x 10^{-4} to 2.8 x 10^{-4} . These are lifetime estimates of the risk from maximum legal exposure just during the preschool years and were calculated for all foods for which tolerances for captan had been granted, assuming exposures at the tolerance limit. They are presented on pages 6, 74 and 75. EPA's recent action reduces the preschooler's maximum legal cancer risk for exposures occurring only until age six from 460 times greater than EPA's "safe" standard of one cancer per million people exposed over their entire lifetimes, to a risk 280 times greater.

tional cancer cases (2.6 \times 10⁻⁴ to 2.9 \times 10⁻⁴) in the preschool population.

2. Using daily intake for all preschoolers in the survey (see footnote 1), UDMH still accounts for the majority of the cancer risk, which is 250 times the level EPA considers acceptable following a full lifetime of exposure.

Letters

(such as Alar), we are ingesting about 10,000 times more natural than synthetic pesticides (1). All plants produce toxins to protect themselves against fungi, insects, and predators such as man (2, 3). Tens of thousands of these natural pesticides have been discovered, and every species of plant contains its own set of different toxins, usually a few dozen. When plants are stressed or damaged, such as during a pest attack, they increase their natural pesticide levels manyfold, occasionally to levels that are acutely toxic to humans (4). Very few of these plant toxins have been tested in animal cancer bioassays, but among those tested, about half (20/42) are carcinogenic (4, 5).

It is probable that almost every plant product in the supermarket contains natural carcinogens. The following foods contain natural pesticides that cause cancer in rats or mice and are present at levels ranging from a few parts per billion to 4 million parts per billion (ppb) (3, 4): anise, apples, bananas, basil, broccoli, Brussels sprouts, cabbage, cantaloupe, carrots, cauliflower, celery, cinnamon, cloves, cocoa, comfrey tea, fennel, grapefruit juice, honeydew melon, horseradish, kale, mushrooms, mustard, nutmeg, orange juice, parsley, parsnips, peaches, black pepper, pineapples, radishes, raspberries, tarragon, and turnips. Of the pesticides we eat, 99.99% are all natural, and, like manmade pesticides, most are relatively new to the modern diet because of the exchange of plant foods among the Americas, Europe, Asia, and Africa within the last 1000 years. It is reassuring, however, that the many layers of general defenses in humans and other animals (1, 6, 7) protect against toxins, without distinguishing whether they are synthetic or natural.

2) Trade-offs. In response to fears about residues of man-made pesticides, plant breeders are active in developing varieties that are naturally pest-resistant. Such varieties contain increased amounts of natural pesticides. It should be no surprise, then, that a newly introduced variety of insectresistant potato had to be withdrawn from the market, due to acute toxicity to humans caused by much higher levels of the teratogens solanine and chaconine than are normally present in potatoes (8). Similarly, a new variety of insect-resistant celery recently introduced widely in the United States is causing outbreaks of dermatitis in produce workers due to a concentration of the carcinogen 8-methoxypsoralen (and related psoralens) of 9000 ppb, rather than the usual 900 ppb (9). Many more such cases are likely to crop up. Thus, there is a fundamental trade-off between nature's pesticides and man-made pesticides. The Environmental Protection Agency (EPA) has strict regulatory requirements for new synthetic pesticides and is steadily weeding out old substances such as Alar that are thought to pose a significant hazard; however, natural pesticides are almost completely neglected. Natural pesticides that are possibly hazardous to humans could easily be decreased by plant breeding.

Given the background of human exposures to natural carcinogens (1–7), the finding that about half the chemicals tested in rodents (whether synthetic or natural) are carcinogenic (1, 5), and the difficulties in risk assessment (discussed below), we have ranked possible hazards on a HERP index (daily Human Exposure dose/Rodent Potency dose, as a percent) in order to achieve some perspective on human exposure to the plethora of carcinogenis (1). Our ranking suggests that carcinogenic hazards from current levels of pesticide residues or water pollution are likely to be minimal relative to the background levels of natural substances.

To put Alar in perspective, we estimate that the possible hazard from UDMH (the carcinogenic breakdown product of Alar) in a daily lifetime glass (6 ounces) of apple juice is HERP = 0.0017% (10). This possible hazard is less than that from the natural carcinogenic hydrazines consumed in one daily mushroom (HERP = 0.1%) (1) or that from aflatoxin in a daily peanut butter sandwich (HERP = 0.03%) (1). It is also less than other possible hazards from natural carcinogens in food, although few have been tested. These include 8-methoxypsoralen in a daily portion (100 grams) of celery (3, 11), allyl isothiocyanate in a daily portion of cabbage or Brussels sprouts (3, 12), and alcohol in a daily glass of orange juice (13). The possible hazard of UDMH in a daily apple is 1/10 that of a daily glass of apple juice. Other HERP comparisons are shown in (1). Apple juice has been reported to contain 137 natural volatile chemicals (14), of which only five have been tested for carcinogenicity (5); three of these-benzyl acetate, alcohol, and acetaldehyde-have been found to be carcinogenic.

The EPA has proposed cancellation hearings on Alar, and the Natural Resources Defense Council (NRDC) is trying to speed this process up by a year or two. The tradeoffs must be considered in efforts to prevent hypothetical carcinogenic risks of 10^{-6} or 10^{-5} , because the results could be counterproductive if the risks of the alternatives are worse. What risks might we incur by banning Alar? Alar is a growth regulator that delays ripening of apples so that they do not drop prematurely, and it also delays overripening in storage. Alar plays a role in reducing pesticide use for some types of apples, particularly in the Northeast (15).

Pesticides, Risk, and Applesauce

The tremendous attention in the media to the growth-regulator Alar raises important issues about the nation's efforts to prevent human cancer by regulating chemicals that are carcinogenic in animal studies. Leslie Roberts, in her Research News articles "Pesticides and kids" (10 Mar., p. 1280) and "Is risk assessment conservative?" (24 Mar., p. 1553), did not address several points that we think are important for putting possible risks in perspective.

1) Pesticides, 99.99% all natural. Although regulatory efforts are focused on identifying and controlling synthetic chemicals that are estimated to pose a possible carcinogenic risk to society greater than one in a million

For example, without Alar, the danger of fruit fall from leafminers is greater, and more pesticides are required to control them. Also, when apples fall prematurely, pests on the apples remain in the orchard to attack the crop the next summer, and more pesticides must be used. Since Alar produces firmer apples, and results in fewer falling to the ground, treated fruit may be less susceptible to molds. Therefore, it is possible that the amounts and variety of mold toxins present in apple juice, for example, parulin (16), will be higher in juice made from untreated apples. The carcinogenicity of patulin has not been adequately examined (17). The EPA should, as NRDC emphasizes, also take into consideration that children consume large amounts of apple juice. Another trade-off is that fewer domestically grown, fresh apples would be available throughout the year, and the price would be higher; thus, consumers might substitute less healthy foods.

3) Risk assessment. Currently, neither theory nor experimental evidence is adequate to guide scientists in extrapolating from rodent cancer tests at the maximum tolerated dose (MTD) to human exposures that are thousands or millions of times lower. Therefore, for prudence's sake, federal regulatory agencies routinely make worst-case assumptions to estimate the upper limit on risk for low doses; however, the real risks at low doses may well be zero. Conventional risk assessments at the low levels of human exposure thus are really quite speculative (1) and should not be viewed as if they were real risks. Accumulating scientific evidence (1, 6, 7, 18) suggests that chemicals administered in animal cancer tests at the MTD are causing cancer in quiescent tissues primarily by increasing cell proliferation, an essential aspect of carcinogenesis for both mutagens and nonmutagens. Because endogenous rates of DNA darnage are enormous (6), cell proliferation alone is likely to be tumorigenic. Cell proliferation converts DNA adducts (either spontaneous or exogenous) to mutations or to epimutations (such as loss of 5methylC) and exposes single-stranded DNA, a much more sensitive target for mutagens. It also allows mutant cells to escape from growth inhibition signals coming from surrounding cells (1, 6, 7).

If animal cancer tests are primarily measuring cell proliferation, then the dose-response curve should fall off sharply with dose, even for mutagens [as with diethylnitrosamine (18)] and should have a threshold for nonmutagens. Thus, the hazards at low doses could be minimal. Furthermore, humans have numerous inducible defense systems against mutagenic carcinogens, such as DNA repair, antioxidant defenses, glutathi-

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one transferases, and so forth, which may make low doses of mutagens protective in some circumstances. Even radiation—the classical DNA-damaging agent and carcinogen-may be protective in small doses against DNA damage at higher doses, as shown by recent work in human cells (19). Also, recent radiation experiments in mice show a dose threshold for the latency of tumor appearance (20). Thus, low doses of carcinogens appear to be both much more common and less hazardous than is generally thought. These scientific questions about mechanisms of carcinogenesis and the preventable causes of human cancer, in any case, are being resolved by the scientific community as quickly as resources allow.

Regulation of low-dose exposures to chemicals based on animal cancer tests may not result in significant reduction of human cancer, because we are exposed to millions of different chemicals-almost all naturaland it is not feasible to test all of them. Most exposures, with the exception of some occupational, medical, or natural pesticide exposures, are at low doses. The selection of chemicals to test, a critical issue, should reflect human exposures that are at high doses relative to their toxic doses and the numbers of people exposed. Epidemiology has been reasonably successful in identifying risk factors for human cancer, such as smoking, hormonal and dietary imbalances, asbestos, and several occupational chemicals; the data suggest that pesticide residues are unlikely to be a significant risk factor (6, 21). Epidemiology, with molecular approaches, is becoming more sophisticated and will continue to be our main tool in analyzing causes of cancer. In order to minimize cancer and the other degenerative diseases of aging [which are associated with our constantly increasing life expectancy (6, 7)], we need to obtain the knowledge that will come from further basic scientific research.

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REFERENCES AND NOTES

- 1. B. N. Ames, R. Magaw, L. S. Gold, Science 236, 271 (1987); ibid. 237, 235 (1987); ibid., p. 1283; B. N. Ames, L. S. Gold, R. Magaw, ibid, p. 1399; B. N. Ames and L. S. Gold, ibid. 238, 1634 (1987); ibid. 240, 1045 (1988).
- 240, 1045 (1760).
 2. B. N. Ames, ibid. 221, 1256 (1983).
 3. R. C. Beier, in Reviews, of Environmental Contamination and Toxicology, G. W. Ware, Ed. (Springer-Variance). Verlag, New York, in press).
- 4. B. N. Ames et al., in preparation.
- L. S. Gold et al., Environ. Health Perspect. 58, 9 (1984); L. S. Gold et al., ibid. 67, 161 (1986); L. S. Gold et al., ibid. 74, 237 (1987); L. S. Gold et al., ibid., in press.

19 MAY 1989

- 6. B. N. Ames, Environ. Mol. Mutagen., in press. in Important Advances in Oncology 1989, V. T.
 DeVita, Jr., S. Hellman, S. A. Rosenberg, Eds.
 (Lippincott, Philadelphia, PA, 1989), pp. 237–247.
 8. S. J. Jadhav, R. P. Sharma, D. K. Salunkhe, CRC
- Crit. Rev. Toxicol. 9, 21 (1981); J. H. Renwick et al., Teratology 30, 371 (1984).
- S. F. Berkley et al., Ann. Intern. Med. 105, 351 (1986); P. J. Seligman et al., Arch. Dermatol. 123, 1277 (1997). 1478 (1987).
- Environmental Protection Agency, "Daminozide special review. Crop field trials. Supplemental daminozide and UDMH residue data for apples, therries, peanuts, pears, and tomatoes," memo from L. Cheng to M. Boodée, 21 February 1989. The HERP is based on a TD 50 of 4.83 mg/kg per day for UDMH. We have not calculated the HERP for Alar (daminozide), which would be much lower, F. Perera and P. Boffetta [J. Natl. Cancer Inst. 80, 1282 (1988)] had reported a HERP for average Alar exposure in apples and apple juice of 0.02%, but this value is too high by a factor of 1000 due to an arithmetic error.

11. The HERP is based on a TD₅₀ of 27.3 mg/kg per day for 8-methoxypsoralen.

 C. H. Van Etten et al., J. Agric. Food Chem. 24, 452 (1976); G. R. Fenwick, R. K. Heaney, W. J. Mullin, Crit. Rev. Food Sci. Nutr. 18, 123 (1983); R. K. Heaney and G. R. Fenwick, J. Sci. Food Agric. 31, 227 (1982). 785 (1980); R. F. Mither, B. G. Lewis, R. K. Heaney, G. R. Fenwick, *Phytochemistry* 26, 1969 (1987). The HERP is based on a TD₅₀ of 96 mg/kg per day for allyl isothiocyanate.

13. E. D. Lund, C. L. Kirkland, P. E. Shaw, J. Agric. Food Chem. 29, 361 (1981). The HERP is based on

- a TD₅₀ of 9100 mg/kg per day for alcohol.

 14. H. Maarse, Ed., Volatile Compounds in Food. Quantitative Data, vol. 2 (Division for Nutrition and Food Research, TNO-CIVO Food Analysis Institute, Zeist, The Netherlands, 1983).
- R. J. Prokopy, Fniit Notes 53, 7 (University of Massachusetts Cooperative Extension, Amherst, MA, 1988).
- 16. C. F. Jelinek, A. E. Pohland, G. E. Wood, J. Assoc. Off. Anal. Chem. 72, 225 (1989); D. M. Wilson, in Mycotoxins and Other Fungal Related Food Problems, J. Wychokins and Other Pungal Related Pool Problems, J. V. Rodricks, Ed. (American Chemical Society, Washington, DC, 1976), pp. 90–109; G. M. Ware, C. W. Thorpe, A. E. Pohland, J. Assoc. Off. Anal. Chem. 57, 1111 (1974); J. L. Wheeler, M. A. Harrison, P. E. Koehler, J. Food Science 52, 479
- 17. International Agency for Research on Cancer, IARC Monographs on the Evaluation of the Cartinogenic Risk of Chemicals to Humans: Some Naturally Occurring and Synthetic Food Components, Furocoumarins and Ultraviolet Radiation (International Agency for Research on Cancer, Lyon, France, 1986), vol. 40, pp. 83-98.
- 18. J. A. Swenberg et al., Environ. Health. Perspect. 76, 57 (1987)
- S. Wolff, V. Afzal, J. K. Wiencke, G. Olivieri, A. Michaeli, Int. J. Radiat. Biol. 53, 39 (1988); K. Sankaranarayanan, A. v. Duyn, M. J. Loos, A. T. Natarajan, Musat. Res. 211, 7 (1989); A. Bosi and G. Olivieri, ibid., p. 13.
- 20. A. Ootsuyama and H. Tanooka, Radiat. Res. 115, 488 (1988).
- A. H. Smith and M. N. Bates, in Carcinogenicity and Pesticides, N. N. Ragsdale and R. Menzer, Eds. (American Chemical Society, Washington, DC, in press); R. Peto, in Assessment of Risks from Low-Level Exposure to Rudiation and Chemicals: A Critical Over-view, A. D. Woodhead, C. J. Shellabarger, V. Pond, A. Hollaender, Eds. (Plenum, New York, NY, 1995) pp. 272-18.
- 1985), pp. 3-16.
 22. We thank M. Profet, T. Slone, and N. Manley for assistance and criticisms. Supported by NCI Outstanding Investigator grant CA39910 to B.N.A., NIEHS Center grant ES01896, and NIEHS/DOE Interagency Agreement Y01-ES-10066.

LETTERS 757 18

DAMINOZIDE

SPECIAL REVIEW

TECHNICAL SUPPORT DOCUMENT
PRELIMINARY DETERMINATION TO CANCEL THE

FOOD USES OF DAMINOZIDE

MAY, 1989

Office of Pesticide Programs

Office of Pesticides and Toxic Substances

United States Environmental Protection Agency

401 M Street, SW

Washington, DC 20460

EXECUTIVE SUMMARY

This document contains the Environmental Protection Agency's (EPA's) evaluation of the risks and benefits of the plant growth regulator daminozide and the basis for the Agency's proposed cancellation of the food uses of daminozide.

Daminozide is the accepted, common name for butanedioic acid mono (2,2-dimethylhydrazide). Daminozide (trade name Alar) was first registered in 1963 by the Uniroyal Chemical Company, Inc., for use on potted chrysanthemums. The first food use of daminozide was registered in 1968 for use on apples. Daminozide is currently registered for use as a plant growth regulator to control vegetative and reproductive growth of orchard crops including apples, cherries, nectarines, peaches, and pears. Daminozide affects flower bud initiation, fruit set and maturity, fruit firmness and coloring, preharvest fruit drop and the market quality of fruit at harvest and during storage. Daminozide is also used to enhance shorter and more erect peanut vines, suppress growth of tomatoes, and modify the stem length and shape of ornamental plants. In 1985, it was estimated that 49-77 percent of the total daminozide usage was on apples, approximately 26 percent of daminozide usage was on peanuts, and 5 percent was on ornamentals. Since 1985, daminozide use on both apples and peanuts has decreased significantly while the non-food uses have remained steady.

on July 18, 1984, EPA issued a Notice of Initiation of a Special Review (which included a Position Document 1 or PD 1) of pesticide products containing daminozide (49 FR 29186). action was based on the Agency finding that pesticide products containing daminozide met the risk criterion relating to oncogenicity formerly at 40 CFR 162.11(a)(3)(ii)(A) and now found at 40 CFR 154.7(a)(2)(i). At that time, the relevant portion of 40 CFR 162.11 provided that a Special Review shall be conducted if the use of a pesticide "induces oncogenic effects in experimental mammalian species or in man as a result of oral, inhalation or dermal exposure...." Specifically, available data indicated that administration of daminozide and its degradate and metabolite, unsymmetrical dimethylhydrazine (UDMH), to laboratory animals resulted in statistically and biologically significant oncogenic responses at multiple organ sites in multiple species and strains of animals. UDMH was believed to be a very potent animal carcinogen and mutagen.

In September 1985, the Agency developed a Draft Notice of Intent to Cancel and a Draft PD 2/3/4 in which cancellation of the food uses of daminozide on the basis of cancer dietary risk

was proposed. The Scientific Advisory Panel (SAP), reviewed the Draft Cancellation Notice and Draft PD 2/3/4 and concluded that the studies relied on by the Agency did not support quantitative cancer risk assessment. The Panel, which was established by Congress to provide scientific review of EPA pesticide actions, believed the data raised concern, but that the studies used by the Agency were sufficiently limited that they were inappropriate for risk assessment.

After consideration of the comments made by the SAP, the Agency decided to postpone any further activity on the cancellation action at that time. However, the Agency did decide to require development of additional data to fully characterize the oncogenic risk of daminozide and UDMH before making any further regulatory decisions. In February 1986, the Agency imposed extensive data requirements on daminozide registrants under section 3(c)(2)(B) of FIFRA. The required data included additional oncogenicity studies, mutagenicity data, plant and animal metabolism studies, livestock feeding data, crop field trials, degradation in food data, storage stability information, market basket surveys, and development of refined, more sensitive detection methodologies.

In the interim period while data were being generated, the Agency determined that certain changes to daminozide registrations intended to reduce human exposure were appropriate. These included: reduced label application rates for apples and limitation of the use on grapes to Concord grapes (not for use as raisins). In addition, the Agency established a lower apple tolerance with a specific expiration date.

By the end of December 1988, much of the required data had been received and reviewed by the Agency. As a result of the review of these data, in particular a 12-month interim sacrifice report of a UDMH oncogenicity study in mice, the Agency has preliminarily determined that dietary exposure to UDMH represents a significant carcinogenic risk which outweighs the benefits of use of daminozide on food crops and therefore warrants the cancellation of the food uses of daminozide. The carcinogenic risk posed by non-dietary exposure to daminozide and UDMH do not outweigh the benefits and are not significant enough to take cancellation action. Therefore, the Agency is proposing that non-food uses be continued without modification of the terms and conditions of registrations.

The Agency has recently evaluated the new Uniroyal data in conjunction with the previously considered (historical) data on daminozide and UDMH in a weight-of-the-evidence determination. Based on this evaluation both daminozide and UDMH were classified

as E2 chemicals, probable human carcinogens. In both the historical studies (NCI 1978; Toth 1977), judged inadequate for risk assessment by the SAP in 1985 and the new Uniroyal studies, daminozide produced vascular and lung tumors in mice. more recent Uniroyal mouse study, daminozide showed a statistically significant increase in hemangiomas/ hemangiosarcomas with increasing dose (Cochran Armitage trend analysis), but not by pairwise comparison (Fisher's exact test a statistical comparison of control and treated animals). A dose-related trend for lung tumors was also seen in male mice. The Agency believes the new data supported by the occurrence of similar tumors in the historical data are sufficient to classify daminozide as a probable human carcinogen. However, the Agency also believes the oncogenic response seen in the daminozide studies is likely caused by the presence of UDMH in the test material and/or metabolic conversion to UDMH.

Vascular and lung tumors seen in the historical UDMH data were also seen in the one-year interim sacrifice in mice from the new Uniroyal study at 80 and 40 ppm. The increase in vascular tumors at 80 ppm was statistically significant by pairwise comparison and trend analysis. UDMH has produced a clear oncogenic response in mice at the highest dose tested and the Agency anticipates that an increase in vascular tumors will also be seen at the lower dose at terminal sacrifice (the 40 ppm dose showed one hemangioma in both a male and female mouse at the one year interim sacrifice).

Neither the Uniroyal rat studies in daminozide (completed) and UDMH (one-year interim sacrifice) or the historical rat data produced treatment related lung or vascular tumors in feeding studies.

The Agency has used data from a 1986 market basket survey, recent crop field trial data, and recently conducted animal feeding studies to estimate exposure for both daminozide and UDMH. From the interim sacrifice report of the UDMH mouse cancer study, the Agency calculated an interim carcinogenic potency factor based on the incidence of hemangiosarcomas (malignant vascular tumors) and combined hemangiomas/hemangiosarcomas of the Based upon this information, the Agency has estimated the lifetime risk of cancer for the general population due to dietary exposure to UDMH to be 4×10^{15} (5 x 10^{15} if an estimate of metabolic conversion of daminozide to UDMH in the gut is considered). (The lifetime risk to the general population [4 x 10⁻⁵] is somewhat lower than the risk cited in the Apple Tolerance Extension document of January 31, 1989 [54 FR 6392] because of a slight overestimate of dietary exposure made in the tolerance document.) The Agency is particularly concerned that a disproportionate share of the lifetime risk occurs from childhood exposure because of the high ratio of food intake per unit bodyweight and the relatively high proportion of a child's diet that is composed of foods which may contain daminozide and UDMH residues. The annual lifetime risk to non-nursing infants (0 to 1 year of age), the highest exposure group, from one year exposure to UDMH is estimated to be approximately 5×10^{-6} (6 \times 10^{-6} if 1 percent metabolic conversion is assumed). The Agency has sought the advice of the National Academy of Science (NAS) as to whether relatively high exposure during infancy and childhood make a person more susceptible to cancer later in life.

The benefits from daminozide use have been assessed in terms of economic impacts which would result if the registered uses of daminozide were cancelled. In assessing benefits, the Agency considered uage information from 1985 and 1988. The Agency concluded the overall impacts from cancellation of daminozide on food uses would be insignificant to minor. Although there are alternatives for some of daminozide's uses, no one alternative chemical provides all the benefits of daminozide. For food uses, the greatest anticipated annual impacts would be in apple production. Estimates of the economic impact on the apple industry are based on 10 percent of the crop treated. Earlier estimates made in conjunction with the apple tolerance extension document of January 31, 1989, referenced a 4 to 8 percent annual crop treatment. The higher estimate (5 to 10 percent) in this document is a result of additional and more in-depth information gathered in the last two months.

Based on 1988 usage data, impacts on the apple use, in terms of net social cost for the whole of society, could range from \$18 - 81 million with the most likely impact approaching the lower end of this range. Growers of Stayman and McIntosh varieties would suffer the greatest individual impact. For other food uses, the annual impacts are anticipated to be approximately \$1.5 - 5.5 million for peaches, approximately \$260,000 for peanuts, and negligible impacts for nectarines, cherries, grapes, and pears. The Agency needs additional information regarding the benefits of daminozide use on tomato transplants and is requesting this information in this document.

The Agency considered a number of options to further reduce dietary exposure and thus reduce carcinogenic risk. In particular, limiting use to certain crops and varieties was considered. None of the considered options was found to reduce the cancer risk such that benefits outweighed risks. Therefore, since the risks of continued use outweigh the benefits, EPA is proposing cancellation of all food uses.

The Agency also considered an emergency suspension of daminozide use on food crops. Although EPA believes that the available data are a cause for concern, the level of risk during the time necessary to complete a cancellation action is not unreasonably high. Also, exposure is expected to decrease as a result of declining use which will further reduce risk.

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The Agency has also examined the risks and benefits of non-dietary exposure. The Agency estimated that the greatest individual lifetime cancer risks posed by non-dietary exposure to UDMH from use on greenhouse ornamentals is 1 x 10°. In addition, the Agency believes that annual grower and consumer losses (as high as \$4.7 million in an industry with an annual wholesale value of \$78.5 to \$104.5 million) would be substantial if the uses of daminozide on ornamentals and bedding plants were cancelled. In this case, the Agency believes that the benefits outweigh the risks for non-dietary use of daminozide on ornamentals and bedding plants. The Agency is proposing that all registrations for use on ornamentals and bedding plants be retained without modifications to the label.

The Agency will also be proposing in the near future the revocation of daminozide tolerances for all raw agricultural commodities as well as the daminozide food and feed additive regulations for processed commodities. No separate tolerances or food and feed additive regulations have been established for UDMH. As noted above, the Agency established a lower tolerance for daminozide on apples with an expiration date while data were being generated. On January 31, 1989 (54 FR 6392; February 10, 1989), the apple tolerance was extended for an additional 18 months to allow the Agency time to complete the Special Review of daminozide.

Uniroyal Chemical Company, Inc World Headquarters Middlebury, CT 06749

January 13, 1989

Mr. David Gelber 60 Minutes CBS-TV 524 West 57th Street New York, New York 10019

Dear David:

re: Daminozide/UDMH

Uniroyal Chemical has studied extensively the safety of daminozide for more than 20 years.

In 20 years of production and use, there is no evidence of adverse health effects among employees, applicators or anyone else exposed to daminozide. The tests originally cited as suggesting a connection between daminozide and health concerns were evaluated by the EPA's Scientific Advisory Panel in 1985 as too unreliable for regulatory decision-making purposes.

New carcinogenicity studies on daminozide, carried out by an independent laboratory under approved EPA test procedures, were completed in 1988. The independent pathologists concluded that daminozide is not carcinogenic in rats or mice. Five separate studies determined that daminozide is not mutagenic.

Since reliable studies on UDYH are not available, Uniroyal Chemical initiated, and is concluding, several lifetime carcinogenicity studies on UDYH, again under approved EPA test procedures. Final results will not be available until late this year. In the meantime, four other studies have proven UDYH is not mutagenic.

Daminozide is an important management tool for growers which allows them to supply high quality, wholesome and nutritious products year round. Daminozide has become an important part of integrated pest management (IPM) programs across the country, reducing the overall need for pesticide use.

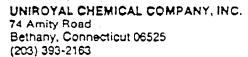
Uniroyal Chemical recognizes that the use of any product may pose some risk, however minute, and the public should evaluate relative risk. Attached is a comparison of the alleged "worst case" risk from lifetime exposure to daminozide and UDMH to common products consumed by the public. The conclusion is obvious; any risk from daminozide or UDMH, if it exists, is negligible.

Sincerely,

Susan Szita Gore

Director, Communications

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THE RELATIVE RISK OF DAMINOZIDE (ALARO/KYLARO) USE

Dr. Bruce Ames, inventor of the widely used Ames Mutagenicity Assay and Professor of Biochemistry at the University of California, Berkeley, has recently published a study which describes the relative risks of a variety of natural and man-made carcinogens. 1/

In this article, Dr. Amos states that rodent cancer tests can't be used to predict absolute human risks. However, they can be used to indicate that some chemicals might be of greater concern than others. He ranks these carcinogenic hazards to humans by an index which relates human exposure to carcinogenic potency. This index is called a HERP INDEX (Human Exposure/Rodent Potency). Dr. Ames stresses the need to identify important causes of cancer among the vast number of minimal risks. This requires knowledge of both the amounts of a substance to which humans are exposed and its carcinogenic potency.

A graphical representation of the relative carcinogenic risk or HERP INDEX for several substances which appear in Dr. Ames' article is attached. The relative carcinogenic risk of these substances which include beer, mushrooms, diet cola, peanut butter, bacon and chlorinated tap water will surprise you. More surprisingly, when a HERP INDEX is calculated for daminozide and its by-product UDME, using worst case results from mouse studies conducted by B. Toth, the relative risk is tenfold lower than tap water.

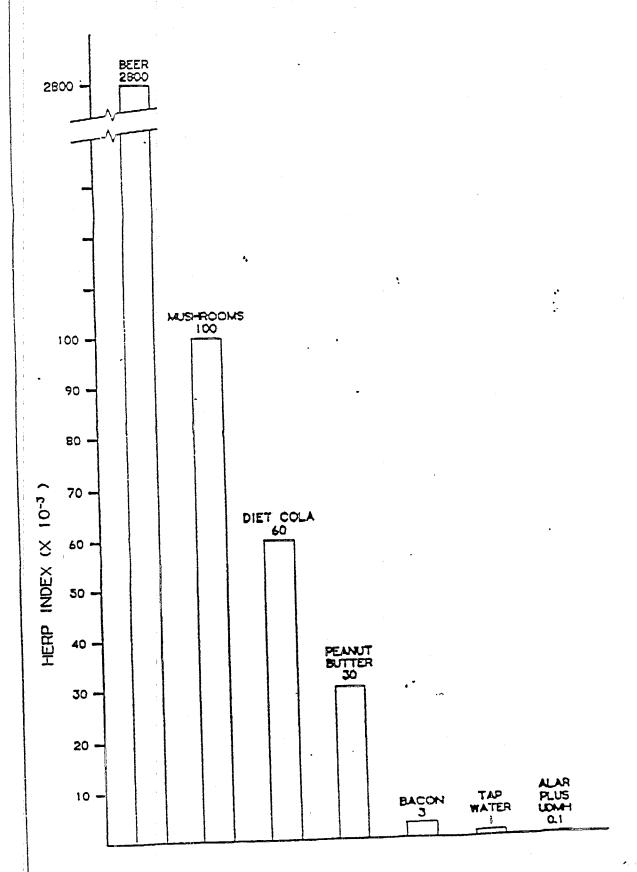
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^{1/} B. N. Ames et al., Ranking Possible Carcinogenic Hazards, Science, Vol. 236; pp. 271-280 (1987).

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Dr. Ames cautions that the HERP INDEX should not be used as a direct estimate of human hazard, since human susceptibility at lower dose rates most likely differ from the high dosage rates that rodents are exposed to. Therefore, the actual hazard or risk at low dose rates might be much less than the HERP values would suggest. He concludes that "... current levels of pesticide residues... are likely to be of minimal concern relative to the background levels of natural substances..."

RELATIVE CARCINOGENIC RISK



Source: https://www.industrydocuments.ucsf.edu/docs/ntbl0000

Be Most Wary of Nature's Own Pesticides

By BRUCE N. AMES

The bad news is that our plant foods contain carcinogens. Carrots, comfrey tea, celery, parsley, parsnips, mushrooms, cabbage, Brussels sprouts, mustard, basil, fennel, orange and grapefruit juices, pepper, cauliflower, broccoli, raspberry and pineapple contain natural pesticides that cause cancer in rats or mice and that are present at levels ranging from 70 ppb (parts per billion) to 4,000,000 ppb—levels that are enormously higher than the amounts of man-made pesticide residues in plant foods.

All plants produce their own natural pesticides to protect themselves against fungi, insects and predators such as man. Tens of thousands of these natural pesticides have been discovered, and every species of plant contains its own set of toxins, usually a few dozen. When plants are stressed or damaged, such as during a pest attack, they increase their natural pesticide levels many fold, occasionally to levels that are acutely toxic to humans.

Only a tiny percentage of these natural pesticides has been tested in animal cancer tests, but of those that have been tested, the percentage that turns out to be carcinogenic is about as high as for man-made pesticides (about 30%). The same appears to be true for natural teratogens (agents that cause birth defects). It is highly probable that almost every plant product in the supermarket contains natural carcinogens and teratogens.

The pesticides that we are eating are 99.99% all natural (we eat 10,000 times more natural than man-made pesticides). Most natural pesticides, like man-made pesticides, are relatively new to the modern diet, because most of our plant foods were brought to Europe within the last 500 years from the Americas, Africa and Asia (and vice versa).

In response to the environmentalist

campaign about tiny traces of man-made pesticides, plant breeders are active in developing varieties that are naturally pest resistant. However, the primary way plant breeders are able to increase natural resistance to pests is to breed plants with increased levels of natural pesticides. It should be no surprise, then, that a newly introduced variety of insect-resistant potato had to be withdrawn from the market, due to acute toxicity to humans caused by much higher levels of the teratogens solanine and chaconine than are normally present in potatoes. Similarly, a new variety of insect-resistant celery recently introduced in the United States had to be withdrawn after it caused widespread outbreaks of dermatitis due to a concentration of carcinogens at 9,000 ppb rather than the usual 900 ppb.

Many more such cases are likely to crop up—they are undetected as yet due to lack of immediate observable effects—because there is a fundamental trade-off between nature's pesticides and man-made pesticides.

The good news is that it now appears from much recent work on the mechanisms of carcinogenesis that the risk of cancer is negligible from carcinogens at levels far below the maximum tolerated dose given to rats and mice in cancer trials. I am not even very concerned about the cancer risk from allyl isothiocyanate, a natural carcinogen present in cabbage at 40,000 ppb and in brown mustard at 900,000 ppb, because I, along with most other leading scientists, am very skeptical about all of these worst-case, low-dose extrapolations from high-dose animal tests.

What must be emphasized is that "the dose makes the poison." For example, consuming five alcoholic drinks per day is clearly a risk factor in humans for cancer, and in pregnant women for giving birth to mentally retarded babies. However, there is no convincing evidence as yet that

consuming one alcoholic drink per day is dangerous. As another example, sunlight can cause cancer, but the evidence suggests that the carcinogenic danger is from repeated sunburns. In fact, ultraviolet light at low doses induces a tan, which protects against the burning of skin by ultraviolet light.

My own estimate for the number of cases of cancer or birth defects caused by man-made pesticide residues in food or water pollution—usually at levels hundreds of thousands or millions of times below that given to rats or mice—is close to zero.

The Food and Drug Administration and the Environmental Protection Agency are doing an adequate job of protecting our food supply from carcinogenic contaminants and are much more credible than the activists lawyers with the Natural Resources Defense Council who spend their time wooing the media with scientifically unfounded claims about the dangers of pesticides, but who have never assembled a knowledgeable board of scientific advisers. The cost to the American public from suchmisplaced efforts is enormous, both in terms of a very large hidden tax on our economy and in terms of lives lost by diverting our resources from real publichealth problems.

In order to minimize cancer and the other degenerative diseases of aging (which are associated with our constantly increasing life expectancy), we need the knowledge that will come from further basic scientific research. Yet we are spending \$70 billion per year on pollution because of wildly exaggerated fears and only \$9 billion per year on all of our basic scientific research.

Bruce N. Ames is chairman of the department of biochemistry and director of the National Institute of Environmental Health Sciences Center at UC Berkeley.

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A Movie Star Pares the Apple Industry

By JOHN NICHOLSON

Hysteria among mothers. School administrators dumping apple juice down the drain, Newsca ers relishing the role of sternly warning America. Action footage on TV of apples being processed mechanically.

That's what took place recently for several weeks, all because of one movie star who decided she wanted to "get involved."

Meryl Streep, who was made famous by her role in the anti-business Silkwood movie, told her friend Robert Redford that she wanted to do something politically as a mother. Redford sent her to a group of which he's a



STREEP

director, called the Natural Resources Defense Council (NRDC), which was supporting (behind the scenes because it's a non-profit 501[c][3] tax-exempt group) a legislative battle to stiffen the pesticide laws last year. "They sent me the [draft] report and I read it and the top of my head came off," Streep recalls.

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the rats' livers; then cancers grew. Continued testing at lower levels is now trying to determine if the cancers grew because of renal failure or because of the chemical.

Meanwhile, because of the scary news, virtually all use in the U.S. of Alar was stopped voluntarily by apple growers after the first test results became known and EPA issued its preliminary warning.

NRDC put into its computers residue levels primarily from FDA's inspectors in southern California—not exactly apple country—and then adjusted them for national rates which augmented the Alar findings. Further, as scientists from the National Food Processors Association have explained, NRDC used an out-of-date potency constant for UDMH, a breakdown component of daminozide.

"This potency constant was based on data acknowledged to be flawed and inappropriate for purposes of risk assessment," NFPA said. "This error alone is expected to lead to a ten-fold overestimate of risk from UDMH exposure."

Regardless, the company's refusal to take Alar off the market until tests are complete to verify

the one case from extremely high dosage has created the aura of industrial obstinacy, fueling Streep's emotional message.

"We firmly believe," says Uniroyal Crop Protection Manager James A. Wylie Jr., "that if we submit to the pressure created by the sensationalism of the media and environmentalists and voluntarily withdraw a product that we honestly believe to not present a risk to public health, then we should not be in this business."

Finally, as the hysteria grew, EPA and the FDA and the USDA's Food and Consumer Services took the highly unusual step of issuing a joint press release. "Data used by NRDC, which claims cancer risks from Alar are 100 times higher than the EPA estimates, were rejected in 1985 by an independent scientific advisory board created by Congress," the release said.

"Not since Orson Welles landed the Martians in New Jersey has an entertainer unleashed such hysteria on the land," wrote Washington Post columnist Jerry Knight. "Streep and her pesticide-paranoid understudies have irreparably damaged the American apple industry, using tactics no less terrorist than poisoning grapes."

"Both consumer and institutional outlets just stopped buying apples [and apple products]," complains Paul S. Weller, president of the Apple Processors Association, a leading trade group. "The government has acted responsibly. Our industry has. The chemical company is acting within the law in good faith. Who's responsible for the financial devastation?

"Maybe it's time for a 'truth-inallegations' law to make these self-appointed guardians of the public health be held personally responsible for the economic consequences of their acts. If Ms. Streep or others were forced to obtain insurance to protect their personal wealth, then perhaps this might rein in their zeal to capitalize on their personal popularity."

That the issue is complex and controversial is proven by EPA's request last year to the National Academy of Sciences to study how to translate animal toxicity findings into possible effects on humans at adult and child levels of use.

"EPA and others have pointed to the lack of scientific validity in the suggestion by the NRDC that the risk is much greater than has been stated by EPA.... Risk estimates for Alar and other pesticides based on animal testing are rough and are not precise predictions of human disease. Because of conservative assumptions used by EPA, actual risks may be lower or even zero," the government said.

In a Washington Post article, Streep explained how she and NRDC devised a new lobbying arm called "Mothers and Others for Pesticide Limits" (as if there were none now). She arranged for a town meeting in her Connecticut village to be televised by "60 Minutes" for instant reaction to the horrible tales to be told by NRDC's paid scientists.

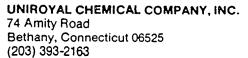
NRDC decided to use Streep to publicize its latest attack on governmental regulators — this time for not adequately considering the effects on children, when relying on animal testing to gauge the effects on humans in evaluating pesticides to be used on foods. To do so, NRDC aimed at several chemicals to determine residues left on the produce, within legal limits, and then extrapolated from those levels what could be regarded as potentially toxic to children.

NRDC hit a public relations bonanza with "Alar"—daminozide produced by Uniroyal. First fingered by EPA in 1985, Alar (or more precisely, its metabolite UDMH) was found in one test of extremely high dosages on rats to ruin

Mr. Nicholson, a Washington free-lance writer, operates a public affairs firm that has done work in the past for several of the major chemical companies producing pesticides.

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SUMMARY OF TOXICOLOGY DATA ON DAMINOZIDE AND UDMH

Review of "Old" Data by EPA and the FIFRA SAP

On September 26, 1985 the FIFRA Scientific Advisory Panel reviewed the then-existing data on daminozide and UDMH to determine the impact of those chemicals on health and the The FIFRA SAP reviewed five studies: Haun 1984, environment. NCI 1978, Toth 1977a, Toth 1977b, and Toth 1973. EPA summarized the FIFRA SAP's recommendation and the Agency's resulting position: "Each of these studies, however, has been examined by the Agency and the FIFRA Scientific Advisory Panel (SAP), and has been found not to provide an adequate basis for regulatory action at this time." 52 Fed. Reg. 1913 (Jan. 16, 1987) (see Appendix EPA subsequently stated that "audits and reviews of these studies have revealed that some of the studies yielded equivocal results and that the other studies have serious flaws or shortcomings in the test methodology and documentation. These facts have led EPA to conclude that the existing studies, singly or in combination, are inadequate to serve as the basis for regulatory action against daminozide under the Federal Insecticide, Fungicide and Rodenticide Act. 52 Fed. Reg. 28257. (July 29, 1987) (see Appendix 6). EPA explained:

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After its review of the studies and critiques, the SAP concluded that, while some of the studies (those performed by Toth, et al.) "give rise to concern about the possible oncogenicity of daminozide," the data are inadequate to allow a qualitative risk assessment of the oncogenic potential of daminozide, i.e., an assessment of how likely it is that daminozide in fact increases the incidence of cancer. The SAP also found that the data are inadequate to allow a quantitative risk assessment.

With respect to UDMH, the SAP found that a recent inhalation study (conducted by Haun, et al.) provides some evidence of potential oncogenicity, but that discrepancies in the study require further clarification. The SAP found use of these data to evaluate dietary risk to be questionable. (A subsequent EPA audit of the inhalation study concluded that it is unusable for regulatory purposes because the source and chemical composition of the test substance could not be determined from the underlying records of the study and because the boiling point of the chemical that was used as the test substance was reported to be some 40 degrees Centigrade higher than that of UDMH.)

52 Fed. Reg. 28257 (Appendix 6). Thus, according to EPA and the FIFRA SAP, the previously existing data do not constitute scientifically valid testing according to generally accepted principles and do not show that daminozide or UDMH is carcinogenic.

Dr. Christopher Wilkinson also has conducted a review of the prior studies. Dr. Wilkinson agrees that:

The results of the older data base provide no compelling evidence that either daminozide or UDMH can be considered rodent carcinogens even at relatively high concentrations. Unfortunately, the data base is notable for its uniformly poor quality and, as pointed out by the EPA's SAP, it is not sufficient for either a qualitative or quantitative

evaluation of oncogenic potential. Base on current GLP requirements and cancer risk assessment guidelines, most of the data would be unacceptable. (See Appendix 2).

Mutagenicity Studies

Daminozide was previously shown to be non-mutagenic in a battery of five studies which included an Ames, E. coli DNA damage, S. cerevisiae genetic damage, mouse lymphoma and mouse dominant lethal assay. EPA requested four additional mutagenicity studies on UDMH. EPA reviewed and accepted as negative three of these studies. These studies are an Ames, CHO chromosome aberration assay and a DNA repair (UDS) assay. A fourth study, a CHO/HPRT gene mutation assay, which originally gave an equivocal result, was repeated and was negative. These data support the conclusion that daminozide and UDMH are non-mutagenic.

Review of New Oncogenicity Studies

Daminozide

Daminozide oncogenicity studies in the rat and mouse were reported by IRDC in August 1988. Daminozide was administered in the diet of Charles River CD-1 mice at dosage levels of 300, 3,000, 6,000 and 10,000 ppm, and in Fischer 344 rats at dosage levels of 100, 500, 5,000 and 10,000 ppm. The text of these reports is given in Appendix 3 and 4. Both reports concluded

that there were no oncogenic effects related to administration of daminozide.

In the daminozide mouse study there was a slight increase in the incidence of pulmonary neoplasms in treated animals and in the incidence of hemangiosarcomas of the liver in male mice. However, these effects were not considered by IRDC to be biologically significant.

The review of the daminozide oncogenicity studies by Dr. Christine Chaisson (Appendix 1) confirms IRDC's conclusion that these studies do not show that daminozide causes cancer. Dr. Chaisson concluded that "with the absence of genotoxic activity and no significant carcinogenic observations, the weight of the evidence clearly favors classification of daminozide as Non-Carcinogenic."

UDMH

UDMH oncogenicity studies conducted by IRDC in the rat and mouse are scheduled to be reported in September 1989. In addition, a very high dose mouse study is scheduled to be reported in January 1990. The schedule for the UDMH studies appresented in the table below:

SCHEDULE FOR UDMH ONCOGENICITY STUDIES

| Animal | Date | Report | Interim |
|---------|---------|--------|------------|
| Species | Started | Dates | Results At |
| Rat | 1/87 | 9/89 | l year |

| Mouse | 1/87 | 9/89 | 8 months, 1 year |
|-------------------------------|------|------|---------------------|
| Mouse (very high doses) | 5/87 | 1/90 | 8 months, 1 year |

Because final results from the UDMH oncogenicity studies are not available, Uniroyal believes that it would be appropriate to reserve decision on UDMH until those results are received and can be evaluated.

Interim results after one year in the UDMH rat and mouse oncogenicity studies indicate no oncogenic effects. (See Appendix 7 and 8). UDMH was administered in water to the rat at dosage levels of 1, 50 and 100 ppm, and to the mouse at dosage levels of 1, 5 and 10 ppm in males and 1, 5 and 20 ppm in females.

In the high dose UDMH mouse oncogenicity study (Appendix 9) where UDMH was administered in water at dosage levels of 40 and 80 ppm, an increase in lung adenomas was found in the high dose treated animals (80 ppm group) as compared to controls at the 8 month interim sacrifice. However, this finding was accompanied by significant liver and blood effects which suggest that the Maximum Tolerated Dose (MTD) was exceeded. A one year interim sacrifice was recently completed. Results show an increase in benign lung tumors in treated vs. control animals. Blood vessel N tumors were also increased in the 80 ppm treated groups. Again, significant toxicity was found in the treated animals which was

accompanied by a marked increase in mortality in the 80 ppm dosage groups vs. control groups. UDMH produced non-neoplastic toxicity to the liver in mid and high dose males and to a lesser degree in females. This hepatotoxicity consisted of accumulation of brown pigment, hypertrophy, single cell necrosis, telangiectasis and hyperplasia of endothelial cells. Biochemical tests were also indicative of liver toxicity, where alanine aminotransferase and sorbitol dehydrogenase levels were significantly elevated in both males and females at 40 and 80 ppm. In addition, males at both 40 and 80 ppm had statistically significant decreases in mean erythrocytes, hemoglobin and hematocrit values at 12 months.

The study also reported an increase in mortality in the 80 ppm dosage group and this was considered a treatment related effect. Survival is summarized in the table below through week 81 of the study.

% SURVIVAL UDMH MOUSE STUDY (High Dose)

| Week of | |) | 4 | 0 | 8 | 0 |
|--------------|----|----------|----|-----------|----|----|
| Study M F | V | | | | | |
| 1.1 | M | <u>F</u> | M | <u>F.</u> | | |
| 52 | 90 | 92 | 90 | 86 | 74 | 78 |
| 71 | 80 | 84 | 80 | 70 | 42 | 48 |
| 77 | 76 | 76 | 76 | 62 | 30 | 40 |
| 81 | 74 | 68 | 68 | 58 | 18 | 30 |

It is evident from the decreased survival, and the liver and blood toxicity observed, that the MTD has been exceeded in this study. A proper evaluation of the carcinogenic potential of UDMH most await the results of the UDMH rat and mouse studies which are being conducted at dosage levels that more closely approximate an MTD.

The interim results from the UDMH studies have been reviewed by Dr. Chaisson. (Appendix 1). Her report states:

Based on preliminary data, the worst-case evaluation would be that UDMH has shown carcinogenic effects in mice when fed overtly toxic levels. The genotoxicity data are negative and do not support the carcinogenicity of UDMH. The preliminary data from the rat studies are negative and do not support the observations in the high-dose mice. The low-dose mouse study, conducted at does which do not compromise the viability of the test animal or drastically alter the basic physiological integrity of the animals, also contradicts the high-dose observations.

The evidence, therefore, suggests that UDMH is not directly expressing carcinogenic potential.

Conclusion

Both the United States Environmental Protection Agency and the FIFRA Scientific Advisory Panel concluded that previously-existing data on daminozide and UDMH were inadequate to classify those chemicals as carcinogens.

The final results of new oncogenicity studies on daminozide in the rat and the mouse do not indicate that daminozide is a carcinogen.

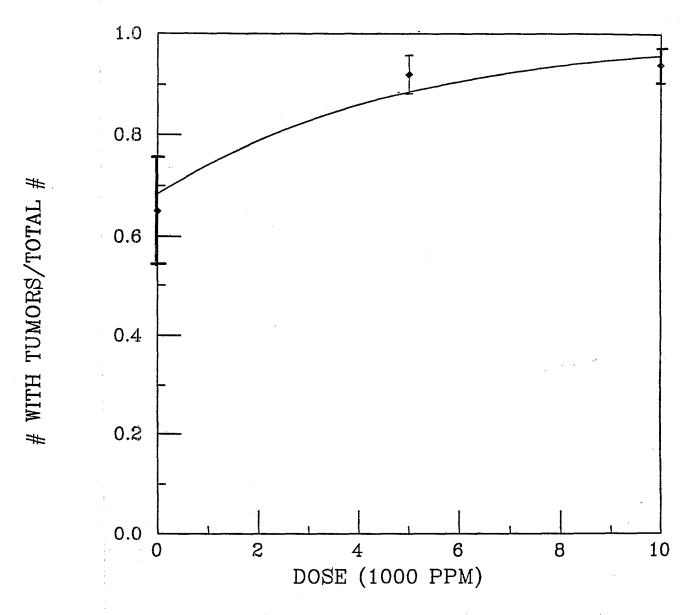
One-year interim results indicate no oncogenic effects in the UDNH rat and mouse studies, and positive interim results in the high dose mouse study are accompanied by indications that the MTD had been exceeded. Evaluation of UDMH should be reserved until the final results of the ongoing studies are available.

Attachment I

GRAPHS OF DATA from NCI/NTP 83

DAMINOZIDE

DAMINOZIDE (NCI/NTP NO 83) (calculated by MSTAGE)



MALE RATS - INTERSTITIAL CELL TUMORS

The "error bars" are the statistical errors (standard deviation) given by $\sqrt[N]{Npq}$: N = No. of animals; p = probability of tumor; q = 1 - p. A line is a good fit if it goes through 2/3 of the error bars.

MALE RATS - INTERSTITIAL CELL TUMORS

| Summary | ο£ | input | data |
|---------|----|-------|------|
|---------|----|-------|------|

| # | Dose value | Numb | | Fisher exact comparison | (Compared | with | control-zero | dose) |
|---|---------------|------|----|-------------------------|-----------|------|--------------|-------|
| | | | | | | | | |
| 1 | 0.000E+00 | 13 | 20 | | | | | |
| 2 | 5.000E+00 | 46 | 50 | 9.491E-03 | | | | |
| 3 | 1.000E+01 | 47 | 50 | 4.241E-03 | 100 | | | |

| Parameter number | Status | Value | Approximate p value | Gradient of logliklihood |
|---------------------|-------------|-----------|------------------------|--------------------------|
| 0 | optimised | 1.150E+00 | 5.986E-03 | -2.975E-14 |
| 1 | optimised | 2.036E-01 | 4.257E-02 | -2.132E-13 |
| 2 | set to zero | 0 | 1.000E+00 | -4.863E+01 |

95.0% one-sided confidence limits (90.0% confidence interval) on stage 1 are: 1.281E-02 to 3.222E-01 (Optimum value: 2.036E-01)

DATA FROM NCI/NTP 83

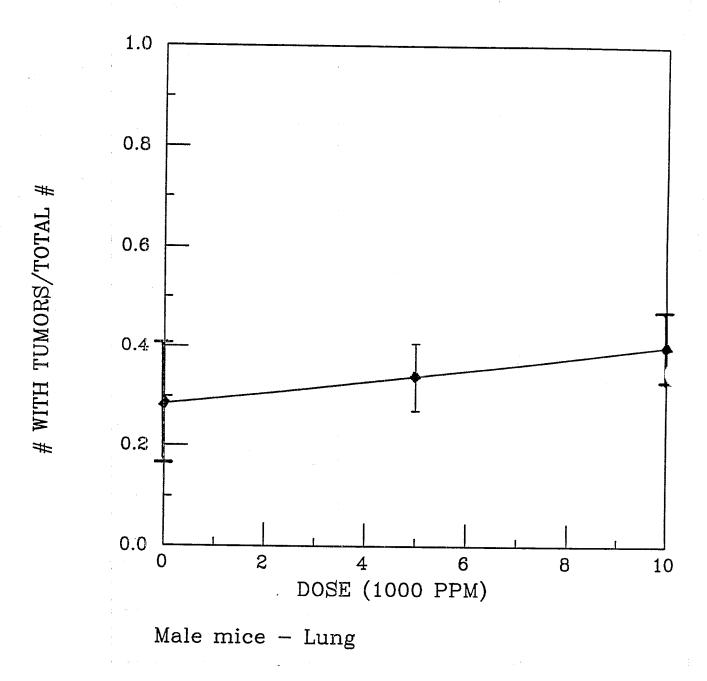
Female rats - Uterus

FEMALE RAT - UTERUS

| | Summary of : Dose | input data Numb | er | Fisher exact |
|---|----------------------|--------------------|--------|--------------|
| # | value | w. tumor | tested | comparison |
| 1 | 0.000E+00 | 0 | 19 | |
| 2 | 5.000E+00 | 7 | 50 | 9.258E-02 |
| 3 | 1.000E+01 | 8 | 50 | 6.421E-02 |

| Parameter number | Status | Value | Approximate p value | Gradient of logliklihood |
|---------------------|-------------|-----------|------------------------|--------------------------|
| 0 | set to zero | 0 | 5.012E-02 | -9.984E+00 |
| 1 | optimised | 2.172E-02 | 5.255E-02 | 0.000E+00 |
| 2 | set to zero | 0 | 1.000E+00 | -4.508E+02 |

95.0% one-sided confidence limits (90.0% confidence interval) on stage 1 are: 0.000E+00 to 3.231E-02 (Optimum value: 2.172E-02)



025546189

MALE MICE - LUNG

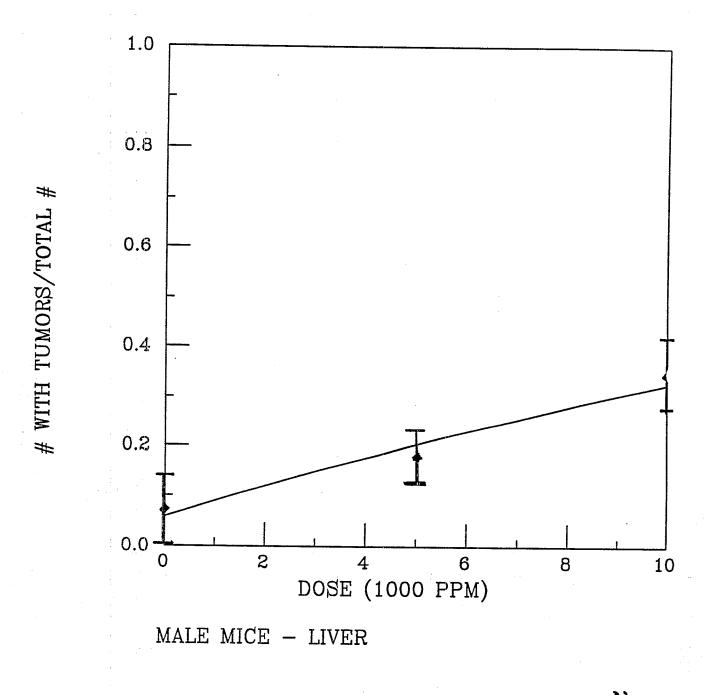
Summary of input data

| Dose | | Numb | er | Fisher exact |
|------|-----------|----------|--------|--------------|
| # | value | w. tumor | tested | comparison |
| | | | | |
| 1 | 0.000E+00 | 4 | 14 | |
| 2 | 5.000E+00 | 17 | 50 | 4.846E-01 |
| 3 | 1.000E+01 | 20 | 50 | 3.247E-01 |

| Parameter number | Status | Value | Approximate p value | Gradient of logliklihood |
|---------------------|-----------|-----------|------------------------|--------------------------|
| 0 | optimised | 3.365E-01 | 3.390E-01 | 2.716E-13 |
| 1 | optimised | 1.418E-02 | 4.160E-01 | -4.814E-12 |
| 2 | optimised | 3.253E-04 | 4.775E-01 | -5.005E-11 |

95.0% one-sided confidence limits (90.0% confidence interval) on stage 1 are: 0.000E+00 to 4.820E-02 (Optimum value: 1.418E-02)

202546190



025546191

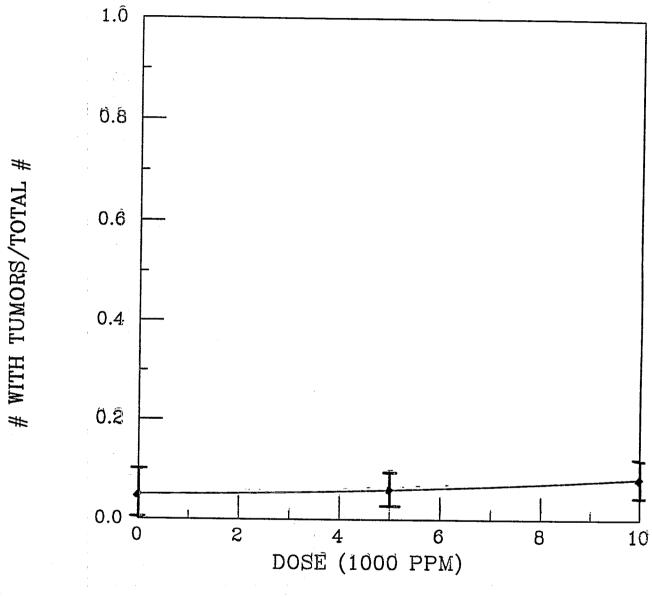
MALE MICE - LIVER

Summary of input data

| Dose | | Numb | er | Fisher exact |
|------|-----------|----------|--------|--------------|
| # | value | w. tumor | tested | comparison |
| | | | | |
| 1 | 0.000E+00 | 1 | 14 | |
| 2 | 5.000E+00 | 9 | 50 | 2.994E-01 |
| 3 | 1.000E+01 | 16 | 46 | 4.037E-02 |

| Parameter number | Status | Value | Approximate p value | Gradient of logliklihood |
|---------------------|-----------|-----------|------------------------|--------------------------|
| 0 | optimised | 6.080E-02 | 6.349E-03 | -8.882E-16 |
| 1 | optimised | 3.350E-02 | 6.349E-03 | -8.882E-15 |
| 2 | fixed | 0 | n.a. | 1.476E+02 |

95.0% one-sided confidence limits (90.0% confidence interval) on stage 1 are: 1.276E-02 to 5.149E-02 (Optimum value: 3.350E-02)



FEMALE RATS - LUNG

025546193

FEMALE RAT - LUNG

| | Summary of i | nput data Numb | er | Fisher exact |
|---|--------------|-------------------|--------|--------------------|
| # | value | w. tumor | tested | comparison |
| 1 | 0.000E+00 | 1 | 20 | ··· |
| 2 | 5.000E+00 | 3 | 50 | 6.787E-01 |
| 2 | 1 0002401 | | 40 | E 27 <i>C</i> W_01 |

| Parameter number | Status | Value | Approximate p value | Gradient of logliklihood |
|---------------------|-----------|-----------|------------------------|-----------------------------|
| 0 | optimised | 5.129E-02 | 4.237E-01 | 4.441E-16 |
| 1 . | optimised | 6.610E-04 | 4.877E-01 | 4.441E-15 |
| 2 | optimised | 2.911E-04 | 4.412E-01 | 2.220E-14 |

95.0% one-sided confidence limits (90.0% confidence interval) on stage 1 are: 0.000E+00 to 1.352E-02 (Optimum value: 6.610E-04)

\$619b\$\$202

INCIDENCE OF PULMONARY NEOPLASMS

| | : | • | | Ma | les | | | | | |
|------------|-------------|-------------|-------------|-----------|---------|-------------|------|-------------|-------------|---|
| 0 p | P83 | 300 | p pe | 3,000 | ppm | 6,000 | ppm | 10,00 | 0 ppm | |
| 300 | SAC (21) | DOS (26) | SAC (24) | DO\$ (26) | | DOS (33) | | DOS (35) | SAC (15) | |
| | ŧ | | ALVEOLA | LR/BRONC | HIOLAR | ADENOMA | S | | | |
| 11 | 9 | 13 | 13 | 10 | 18 | 18 | 13 | 19 | 8 | |
| | • | A | LVEOLAF | k/Bronch | IOLAR C | CARCINOM | AS . | | | |
| 3 | 2 | 1 | i | · 1 | 4 | 4 | 3 | 6 | 0. | |
| | * | | TOTAL | PULHON | ARY NEC | PLASMS | | | | |
| 14 | . 11 | 14 | 14 | 11 | 22 | 22 | 16 | 25 | 8 | |
| | | | | Fem | ales | | | | | |
| (27) | (23) | (31) | (19) | (25) | (25) | (29) | (21) | (31) | (19) | |
| | ÷. · | • . | ALVEOLA | R/Bronc | HIOLAR | ADENOMA | S | | | |
| 8 | 12 | 14 | 12 | 12 | 15 | 12 | 16 | 13 | 13 | |
| | | A | LVEOLAR | /BRONCH | IOLAR C | ARCINOM | AS | | | |
| 0 | 0 | 3 | 0 | 2 | 0 | 2 | 0 | 4 | 0 | |
| | | | TOTAL | PULMON | ARY NEC | PLASMS | | • | | į |
| 8 | 12 | 17 | 12 | 14 | 15 | 14 | 16 | 17 | 13 | |

Lung tumors occur spontaneously in many strains of mice and the incidence varies between strain with a higher incidence in the males compared to the females. The neoplasms appear to arise either from the alveolar cells lining the pulmonary alveoli or from Clara cells found normally within bronchioles. Since these two types of lung neoplasms cannot be easily distinguished between at the light microscopic level, they are usually designated as alveolar/bronchiolar adenomas or carcinomas. The incidence varies quite markedly between different studies conducted in the same strain of mice in

the same laboratory. The historical incidence of alveolar/bronchiolar adenomas and carcinomas in four, two-year chronic studies conducted at IRDC from 1983 to 1985 is presented below.

HISTORICAL INCIDENCE (I) OF PULMORARY NEOPLASMS IN CD-1 MICE AT IRDC

| Study | Males | | Total | Females | | Total |
|-------|----------|------------|-------|----------|------------|-------|
| | Adenomas | Carcinomas | | Adenomas | Carcinomas | |
| A | 18.2 | 0.90 | 19.1 | 12.7 | 4.5 | 17.2 |
| 3 | 44.0 | 0 | 44.0 | 22.0 | 2.0 | 24.0 |
| С | 28.0 | 6.0 | 34.0 | 14.0 | 2.0 | 16.0 |
| D | 26.1 | 8.7 | 34.8 | 8.7 | 2.9 | 11.6 |

3. Summary

A variety of nonneoplastic and neoplastic lesions were seen in both sexes across dose levels and the majority of them appeared to not be related to the administration of the test article. Inflammation and brown pigment in the livers of the male mice were more prevalent in the treated than in the controls and may have been related to the administration of the test article. An increase in lung neoplasms was present in both the treated males and treated females compared to the controls. A dose response, however, was not evident.

Prepared By:

Frith, D.V.M., Ph.D.

Robert G. Geil, D.V.M., A.C.V.P. Diplomate Scientific Director of Pathology Division

399-054

DAKINOZIDE

SPECIAL REVIEW

TECHNICAL SUPPORT DOCUMENT
PRELIMINARY DETERMINATION TO CANCEL THE

FOOD USES OF DAMINOZIDE

MAY, 1989

Office of Pesticide Programs

Office of Pesticides and Toxic Substances

United States Environmental Protection Agency

401 M Street, SW

Washington, DC 20460

EXECUTIVE SUMMARY

This document contains the Environmental Protection Agency's (EFA's) evaluation of the risks and benefits of the plant growth regulator daminozide and the basis for the Agency's proposed cancellation of the food uses of daminozide.

Daminozide is the accepted, common name for butanedioic acid mono (2,2-dimethylhydrazide). Daminozide (trade name Alar*) was first registered in 1963 by the Uniroyal Chemical Company, Inc., for use on potted chrysanthemums. The first food use of daminozide was registered in 1968 for use on apples. Daminozide is currently registered for use as a plant growth regulator to control vegetative and reproductive growth of orchard crops including apples, cherries, nectarines, peaches, and pears. Daminozide affects flower bud initiation, fruit set and maturity, fruit firmness and coloring, preharvest fruit drop and the market quality of fruit at harvest and during storage. Daminozide is also used to enhance shorter and more erect peanut vines, suppress growth of tomatoes, and modify the stem length and shape of ornamental plants. In 1985, it was estimated that 49-77 percent of the total daminozide usage was on apples, approximately 26 percent of daminozide usage was on peanuts, and 5 percent was on ornamentals. Since 1985, daminozide use on both apples and peanuts has decreased significantly while the non-food uses have remained steady.

On July 18, 1984, EPA issued a Notice of Initiation of a Special Review (which included a Position Document 1 or PD 1) of pesticide products containing daminozide (49 FR 29186). action was based on the Agency finding that pesticide products containing daminozide met the risk criterion relating to oncogenicity formerly at 40 CFR 162.11(a)(3)(ii)(A) and now found at 40 CFR: 154.7(a)(2)(i). At that time, the relevant portion of 40 CFR 162.11 provided that a Special Review shall be conducted if the use of a pesticide "induces oncogenic effects in experimental mammalian species or in man as a result of oral, inhalation or dermal exposure..." Specifically, available data indicated that administration of daminozide and its degradate and metabolite, unsymmetrical dimethylhydrazine (UDMH), to laboratory animals resulted in statistically and biologically significant oncogenic responses at multiple organ sites in multiple species and strains of animals. UDMH was believed to be a very potent animal carcinogen and mutagen.

In September 1985, the Agency developed a Draft Notice of Intent to Cancel and a Draft PD 2/3/4 in which cancellation of the food uses of daminozide on the basis of cancer dietary risk

was proposed. The Scientific Advisory Panel (SAP), reviewed the Draft Cancellation Notice and Draft PD 2/3/4 and concluded that the studies relied on by the Agency did not support quantitative cancer risk assessment. The Panel, which was established by Congress to provide scientific review of EPA pesticide actions, believed the data raised concarn, but that the studies used by the Agency were sufficiently limited that they were inappropriate for risk assessment.

After consideration of the comments made by the SAP, the Agency decided to postpone any further activity on the cancellation action at that time. However, the Agency did decide to require development of additional data to fully characterize the photogenic risk of daminozide and UDMH before making any further regulatory decisions. In February 1986, the Agency imposed extensive data requirements on daminozide registrants under section 3(c)(2)(B) of FIFRA. The required data included additional oncogenicity studies, mutagenicity data, plant and animal metabolism studies, livestock feeding data, crop field trials, degradation in food data, storage stability information, market basket surveys, and development of refined, more sensitive detection methodologies.

In the interim period while data were being generated, the Agency determined that certain changes to daminozide registrations intended to reduce human exposure were appropriate. These included: reduced label application rates for apples and limitation of the use on grapes to Concord grapes (not for use as raisins). In addition, the Agency established a lower apple tolerance with a specific expiration date.

By the end of December 1988, much of the required data had been received and reviewed by the Agency. As a result of the review of these data, in particular a 12-month interim sacrifice report of a UDMH oncogenicity study in mice, the Agency has preliminarily determined that dietary exposure to UDMH represents a significant carcinogenic risk which outweighs the benefits of use of daminozide on food crops and therefore warrants the cancellation of the food uses of daminozide. The carcinogenic risk posed by non-dietary exposure to daminozide and UDMH do not outweigh the benefits and are not significant enough to take cancellation action. Therefore, the Agency is proposing that non-food uses be continued without modification of the terms and conditions of registrations.

The Agency has recently evaluated the new Uniroyal data in conjunction with the previously considered (historical) data on daminozide and UDMH in a weight-of-the-evidence determination. Based on this evaluation both daminozide and UDMH were classified

as E2 chemicals, probable human carcinogens. In both the historical studies (NCI 1978; Toth 1977), judged inadequate for risk assessment by the SAP in 1985 and the new Uniroyal studies, daminozide produced vascular and lung tumors in mice. more recent Uniroyal mouse study, daminozide showed a statistically significant increase in hemangiomas/ hemangiosarcomas with increasing dose (Cochran Armitage trend analysis), but not by pairwise comparison (Fisher's exact test a statistical comparison of control and treated animals). A dose-related trend for lung tumors was also seen in male mice. The Agency believes the new data supported by the occurrence of similar tumors in the historical data are sufficient to classify daminozide as a probable human carcinogen. However, the Agency also believes the oncogenic response seen in the daminozide studies is likely caused by the presence of UDMH in the test material and/or metabolic conversion to UDMH.

Vascular and lung tumors seen in the historical UDMH data were also seen in the one-year interim sacrifice in mice from the new Uniroyal study at 80 and 40 ppm. The increase in vascular tumors at 80 ppm was statistically significant by pairwise comparison and trend analysis. UDMH has produced a clear oncogenic response in mice at the highest dose tested and the Agency anticipates that an increase in vascular tumors will also be seen at the lower dose at terminal sacrifice (the 40 ppm dose showed one hemangioma in both a male and female mouse at the one year interim sacrifice).

Neither the Uniroyal rat studies in daminozide (completed) and UDMH (one-year interim sacrifice) or the historical rat data produced treatment related lung or vascular tumors in feeding studies.

The Agency has used data from a 1986 market basket survey, recent crop field trial data, and recently conducted animal feeding studies to estimate exposure for both daminozide and UDMH. From the interim sacrifice report of the UDMH mouse cancer study, the Agency calculated an interim carcinogenic potency factor based on the incidence of hemangiosarcomas (malignant vascular tumors) and combined hemangiomas/hemangiosarcomas of the liver. Based upon this information, the Agency has estimated the lifetime risk of cancer for the general population due to dietary exposure to UDMH to be 4×10^{15} (5 x 10^{15} if an estimate of metabolic conversion of daminozide to UDMH in the gut is considered). (The lifetime risk to the general population [4 x 10.5] is somewhat lower than the risk cited in the Apple Tolerance Extension document of January 31, 1989 [54 FR 6392] because of a slight overestimate of dietary exposure made in the tolerance document.) The Agency is particularly concerned that a disproportionate share of the lifetime risk occurs from childhood exposure because of the high ratio of food intake per unit bodyweight and the relatively high proportion of a child's diet that is composed of foods which may contain daminozide and UDMH residues. The annual lifetime risk to non-nursing infants (0 to 1 year of age), the highest exposure group, from one year exposure to UDMH is estimated to be approximately 5 x 10 (6 x 10 if 1 percent metabolic conversion is assumed). The Agency has sought the advice of the National Academy of Science (NAS) as to whether relatively high exposure during infancy and childhood make a person more susceptible to cancer later in life.

The benefits from daminozide use have been assessed in terms of economic impacts which would result if the registered uses of daminozide were cancelled. In assessing benefits, the Agency considered uage information from 1985 and 1988. The Agency concluded the overall impacts from cancellation of daminozide on food uses would be insignificant to minor. Although there are alternatives for some of daminozide's uses, no one alternative chemical provides all the benefits of daminozide. For food uses, the greatest anticipated annual impacts would be in apple production. Estimates of the economic impact on the apple industry are based on 10 percent of the crop treated. Earlier estimates made in conjunction with the apple tolerance extension document of January 31, 1989, referenced a 4 to 8 percent annual crop treatment. The higher estimate (5 to 10 percent) in this document is a result of additional and more in-depth information gathered in the last two months.

Based on 1988 usage data, impacts on the apple use, in terms of net social cost for the whole of society, could range from \$18 - 81 million with the most likely impact approaching the lower end of this range. Growers of Stayman and McIntosh varieties would suffer the greatest individual impact. For other food uses, the annual impacts are anticipated to be approximately \$1.5 - 5.5 million for peaches, approximately \$260,000 for peanuts, and negligible impacts for nectarines, cherries, grapes, and pears. The Acency needs additional information regarding the benefits of daminozide use on tomato transplants and is requesting this information in this document.

The Agency considered a number of options to further reduce dietary exposure and thus reduce carcinogenic risk. In particular, limiting use to certain crops and varieties was considered. None of the considered options was found to reduce the cancer risk such that benefits outweighed risks. Therefore, since the risks of continued use outweigh the benefits, EPA is proposing cancellation of all food uses.

The Agency also considered an emergency suspension of daminozide use on food crops. Although EPA believes that the available data are a cause for concern, the level of risk during the time necessary to complete a cancellation action is not unreasonably high. Also, exposure is expected to decrease as a result of declining use which will further reduce risk.

The Agency has also examined the risks and benefits of non-dietary exposure. The Agency estimated that the greatest individual lifetime cancer risks posed by non-dietary exposure to UDMH from use on greenhouse ornamentals is 1 x 10.6. In addition, the Agency believes that annual grower and consumer losses (as high as \$4.7 million in an industry with an annual wholesale value of \$78.5 to \$104.5 million) would be substantial if the uses of daminozide on ornamentals and bedding plants were cancelled. In this case, the Agency believes that the benefits outweigh the risks for non-dietary use of daminozide on ornamentals and bedding plants. The Agency is proposing that all registrations for use on ornamentals and bedding plants be retained without modifications to the label.

The Agency will also be proposing in the near future the revocation of daminozide tolerances for all raw agricultural commodities as well as the daminozide food and feed additive regulations for processed commodities. No separate tolerances or food and feed additive regulations have been established for UDMH. As noted above, the Agency established a lower tolerance for daminozide on apples with an expiration date while data were being generated. On January 31, 1989 (54 FR 6392; February 10, 1989), the apple tolerance was extended for an additional 18 months to allow the Agency time to complete the Special Review of daminozide.

2023346203

REGULATORY DECISION-MAKING UNDER UNCERTAINTY: THE CASE OF ALAR*

* This is a teaching case commissioned by the Harvard Center for Risk Analysis for use by the Office of Continuing Education, Harvard School of Public Health, for a course on Risk Analysis in Environmental & Occupational Health, September 5-7, 1990. The case was written by Ms. Susan Moses under the supervision of Dr. John D. Graham.

As Jack Moore, Acting Administrator of the U.S. Environmental Protection Agency (EPA), hung up the phone, he wondered whether he should agree to an interview with Ed Bradley for a 60 Minutes segment on pesticides.

It was January 1989, George Bush had just been inaugurated as President, and the Administration had not put forth its policies on environmental issues. Jack Moore was Acting Administrator of He had most recently held the position of Assistant EPA. Administrator for Pesticides and Toxic Substances at EPA. advocate for the use of sound science in the regulatory decisionmaking process, he had good working relationships with both industry and environmentalists alike. Twice before Dr. Moore had been asked to appear on 60 Minutes (prior to being in the position of Acting Administrator), and both times he declined. He was under no pressure from The White House; it was his decision whether to grant the interview or not. Not too long ago, Dr. Moore had received an informal copy of a not-yet-released report on pesticides in children's food, written by the Natural Resources Defense Council (NRDC), an advocacy group. He now began to wonder whether or not there might be some connection between this report and the scheduled 60 Minutes segment, particularly since Ed Bradley had referred to the pesticide Alar, a registered trademark for the chemical daminozide that is sprayed on apples. Alar, and its metabolite unsymmetrical dimethylhydrazine (UDMH), were highlighted in the NRDC report as potential hazards.

Knowing that <u>60 Minutes</u> is watched by millions of viewers, Jack Moore began to evaluate the implications of his appearance on the show and wondered how he should prepare himself if he agreed to the interview with Ed Bradley.

THE FEDERAL INSECTICIDE, FUNGICIDE, AND RODENTICIDE ACT (FIFRA)

The Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA), enacted in 1947, is the federal law regulating pesticide products and their use in the United States. Until 1972, the law focused on the proper labeling of pesticide products. In 1972, amendments were passed changing FIFRA from a labeling law to a more comprehensive statute that charged EPA with the responsibility of premarket data review and registration. These changes reflected public concern about potential adverse health effects and the need to evaluate the "reasonableness" of any of these risks. Since 1972 there have been a series of FIFRA amendments, and the debate over the adequacy of the current law in protecting human health and the environment continues today.

FIFRA is a "risk-balancing" statute. EPA weighs any potential adverse effects of the product against its benefits as part of the decision-making process. The operating words of the statute are that the pesticide, when used as directed, "will not cause any unreasonable risk to man or the environment, taking into account the economic, social, and environmental costs and benefits of the use of the pesticide." This risk/benefit mandate is in contrast

to other laws, such as the Delaney Clause of the Federal Food, Drug, and Cosmetic Act, which bans the use of any intentional food additive that is shown to be a carcinogen in humans or animals, regardless of any benefits.

All pesticide products must be registered by EPA prior to being marketed and distributed in commerce. Manufacturers must submit toxicological and environmental data to the Agency as part of their application for product registration. EPA reviews these data for short-term and long-term toxicity, mutagenicity, oncogenicity, fetotoxicity, teratogenicity, for effects on wildlife and other organisms, and for environmental fate and residues in food or feed.

Under the Federal Food, Drug, and Cosmetic Act, EPA sets tolerances for pesticide residues in food. A tolerance is the maximum level of residue permitted in the raw harvested commodity and on processed forms of the commodity.

If EPA approves a pesticide registration application, the product may be manufactured for commerce. However, each product is approved to control specific pests, for use on specific crops, and for use in specific concentrations and frequency of application.

All pesticides that were on the market prior to the enactment of FIFRA were "grandfathered" under the statute. Therefore, it is possible that many of these products would not be approved today under the current pesticide registration procedure. However, EPA is in the process of reviewing these "existing" pesticides to

determine whether any of them should be withdrawn from the market because of potential harmful effects. The Agency is under Congressional pressure to move more quickly in its evaluation of these grandfathered substances.

The burden of proof as to the "safety" of a new pesticide rests with the manufacturer submitting the registration application. If for whatever reason the Agency determines that the terms of the registration are not being met, EPA may begin the "Special Review" process for canceling the registration. At this point, the burden of finding "unreasonable risk" is shifted to the Agency.

This review is a process, formerly called the Rebuttable Presumption Against Registration (RPAR), whereby EPA collects and evaluates information on the pesticide and can request additional information from the manufacturer to determine whether any uses of the pesticide "cause unreasonable adverse effects to human health or the environment."

Depending on the nature of the new data, the Agency may propose changes to the terms of the registration under the rationale that such changes reduce risks to the level where the benefits outweigh the risks; or, EPA may proceed with cancellation by issuing a "Notice of Intent to Cancel" if the Agency finds that the risks outweigh the benefits. Throughout this entire process, the public has the opportunity to submit comments in an effort to affect any regulatory action.

THE SCIENTIFIC ADVISORY PANEL (SAP)

The Scientific Advisory Panel (SAP), a standing advisory committee, was mandated in 1975 by FIFRA to review, for potential regulatory action, EPA's evaluations of environmental and health risks posed by specific pesticides.

Regulatory History of Alar

Alar, the Uniroyal Chemical Company trade name for daminozide, was first registered with the Environmental Protection Agency (EPA) as a plant growth regulator for potted chrysanthemums in 1963. The first registered food use was for apples in 1968. To apple growers, Alar was a major breakthrough; ripe apples stayed on the tree longer, and remained firmer and redder (better market quality) during harvest and storage. The tolerance (maximum permissible residue level) for Alar in apples was set at 30 ppm. From 1968-1985 Alar was also registered for use on cherries, nectarines, peaches, pears, grapes, peanuts, tomatoes, and ornamental plants. However, in 1985 it was estimated that approximately 75% of the daminozide in commerce was used on apples; since that time usage has declined significantly (EPA, 1989).

In the summer of 1984, EPA issued a Notice of Initiation of a Special Review of pesticide products containing daminozide, which indicated that the Agency was going to investigate potential harmful effects of the pesticide. Of particular concern was a

degradation product of daminozide, unsymmetrical dimethylhydrazine (UDMH). Data from animal studies indicated that both daminozide and UDMH elicited "statistically and biologically significant oncogenic responses at multiple organ sites in multiple species and strains of animals. UDMH was believed to be a very potent animal carcinogen and mutagen." (EPA, 1989) Although the database was limited, the Agency decided to proceed with a cancellation action.

A year later, in the fall of 1985, EPA developed a combined Preliminary and Final Determination and Draft Cancellation Notice. The process was accelerated in light of the potentially high dietary exposure of daminozide and UDMH to children.

The EPA Scientific Advisory Panel (SAP), required under FIFRA to review this documentation, believed that while the data raised concerns, they were not sufficient to support a quantitative risk assessment for either daminozide or UDMH. The Department of Agriculture (USDA) also reviewed the report and argued that EPA had underestimated the benefits of daminozide use, and therefore, should reassess its call for cancellation. Although not legally bound by the SAP decision, the Agency decided to reassess its position based on the SAP recommendation, and chose not to proceed with the cancellation action. The Agency did require Uniroyal to conduct additional testing and collect additional data on the oncogenic risk of daminozide and UDMH. In the interim, to reduce exposure, EPA lowered the tolerance for daminozide residues on apples from 30 ppm to 20 ppm. However, this tolerance was set to

expire on July 31, 1987 at which time EPA believed it would have additional data to evaluate the tolerance further. The Agency also instructed Uniroyal to include a use advisory with its product warning not to use the chemical on apples intended for use in apple sauce and apple juice. (When apples are processed into apple sauce and juice, the heating process causes daminozide to break down into UDMH. Therefore, these products have higher concentrations of UDMH.)

At the time, Jack Moore felt that there was enough evidence for EPA to be concerned about the carcinogenic potential of daminozide and its metabolite UDMH, but not enough from a legal point of view to regulate Alar under FIFRA. Unlike the requirements for new pesticides where the registrant must bear the burden of proof that "the intended use will not present an unreasonable risk," for currently registered chemicals such as daminozide, the burden of finding "unreasonable risk" lay with EPA.

In 1985-86, when the carcinogenic potential of Alar was made public, consumers acted predictably—they stopped buying apples until they were assured by their grocers and food processors that the apples in their stores and products were Alar-free. The protest was relatively calm, and short-lived.

Over the next several years (1986-88), NRDC, Public Citizen, and the States of New York and Maine petitioned and then sued EPA for not amending the tolerance for daminozide residue to zero. The Agency claimed it did not have sufficient data to determine



benefits attributed to daminozide" (many of which relate to the appearance of the fruit). The overall effect on all growers is estimated to be "an annual income increase of \$1.5 million" resulting from higher market apple prices, with daminozide users losing \$14.5 million and non-users gaining \$16.1 million. Growers of certain apple varieties (particularly Eastern McIntosh and Stayman), however, may experience annual income losses of \$5.7 and \$1.8 million, respectively.

In addition, a cancellation of Alar was estimated to reduce the supply of fresh apples. "The net social cost (total society cost) of cancellation of daminozide use on apples based on 10 percent of the crop treated is estimated to range from \$18 to \$81 million as compared to \$44 to \$198 million for 1985 usage levels. Economic impacts of a cancellation for other uses of daminozide, such as on cherries, grapes, peanuts, and ornamentals, are predicted to be much less significant. In addition to the apple industry, peach growers' losses were estimated to range from \$1.5 to \$5.5 million (EPA, 1989).

The Agency staff did not recommend issuing an emergency suspension of daminozide use on food crops because while the data did indicate cause for concern, "the level of risk during the time necessary to complete a cancellation action is not unreasonably high." (EPA, 1989). According to FIFRA, an immediate suspension is warranted only if EPA determines that the risks present an immediate hazard. In the interim it was also expected that usage would decline, thereby lowering the risk of exposure.

RISK ASSESSMENT DATA

In historical studies from 1977-78, as well as more recent data submitted by Uniroyal, daminozide produced vascular and lung tumors in mice. However, this oncogenic response may be linked to the presence of UDMH in the test material (possibly by metabolic conversion). UDMH also produced vascular and lung tumors. On the other hand, the data from rat studies for both daminozide and UDMH is less significant. More specific information on these studies is shown in Table 1.

The estimates of daminozide and UDMH residues in raw and produced foods are shown in Tables 2 and 3. The estimates of dietary exposure for the U.S. population as well as for specific age subsets are shown in Tables 4-9.

The lifetime risk of cancer for the general population due to dietary exposure to UDMH was estimated to be $4-5 \times 10-5$. However, because children have a high ratio of food intake for their bodyweight and because such a high proportion of their diet comes from foods that may have high levels of daminozide and/or UDMH residues, a cancer risk of $5-6 \times 10-6$ was estimated.

THE NRDC REPORT

The NRDC study, "Intolerable Risk: Pesticides in our Children's Food" examined the levels of pesticide residues found

in fruits and vegetables to determine whether they presented a health hazard to preschoolers. The NRDC report quantified the preschooler's dietary exposure to 23 pesticide residues in 27 food items as well as the resultant potential health risks in terms of two endpoints—cancer and disruption in central nervous system functioning.

The principal findings of the study were that

"Preschoolers are being exposed to hazardous levels of pesticides in fruits and vegetables. Between 5,500 and 6,000 (a risk range of 2.5 x 10 to 2.8 x 10) of the current population of American preschoolers may eventually get cancer solely as a result of their exposure before six years of age to eight pesticides or metabolites commonly found in fruits and vegetables." (NRDC report, p.2)

The report singled out UDMH as "the greatest source of the cancer risk identified by NRDC." This risk was estimated as "240 times greater than the cancer risk considered acceptable by EPA following a full lifetime of exposure;" one out of 4000 children will get cancer as a result of ingesting Alar-treated apples.

The report also recommended that Congress amend the current pesticide regulations to "close loopholes in EPA's and FDA's regulatory programs." Furthermore, NRDC raised concerns about how long it takes to lower tolerances or remove hazardous pesticides from the market, and recommended that EPA be granted the authority to take action more quickly. (The Executive Summary of the NRDC report is attached.)

REGULATORY ACTION

With his staff's data analyses and recommendations in hand, the current tolerance on Alar in apples due to expire January 31, 1989, and the findings of the NRDC report soon to be released, Jack Moore had to make a decision on Alar in addition to deciding whether or not to be interviewed for 60 Minutes.

STUDY QUESTIONS

- 1. Should Jack Moore appear on 60 Minutes? Discuss the pros and cons of this decision, taking into account the fact that he is Acting Administrator of EPA.
- 2. If he agrees to the interview, how should Jack Moore prepare himself?
- 3. What regulatory decision should the Agency make on Alar? Should Jack Moore reveal this decision during his 60 Minutes interview?
- 4. In addition to "Why hasn't EPA banned Alar?" and "Is the current law adequate to protect the public from the risks of pesticides?", what additional questions should Jack Moore anticipate, and how should he respond?
- 5. What factors in addition to the "scientific facts" must Jack Moore consider in his decision-making concerning Alar?
- 6. Is the current law adequate to protect the public from the risks of pesticides?

TABLE 1

NEOPLASTIC RESPONSE REPORTED FOR DAMINOZIDE AND UDMH IN RODENT CARCINOGENICITY STUDIES

| Study Name | Species & Route | Tumor Site and Potency (if Calculated) |
|--------------------|---------------------------------------|--|
| DAMINOZ:DE | | |
| Toth, 1977 | Swiss mouse (drinking water) | Blood vessel sarcomas in males and females; alveolar/bronchiolar adenomas and carcinomas in males and females; kidney tumors in males |
| NCI, 1978a | B6C3F ₁ mouse (dietary) | Liver carcinomas in males; alveolar/ bronchiolar carcinomas and adenomas in males and females |
| NCI, 1978b | F344 rat (dietary) | Uterine endometrial adenocarcinomas and leiomyosarcomas in females |
| Uniroyal, 1988a | CD-1 mouse (dietary) | Dose-related trend with regard to blood vessel tumors of liver in males and females; dose-related increase in alveolar/bronchiolar adenomas in males and females; no increases in vascular or lung tumors by pairwise comparison |
| UDMH | | lung tumors by pairwise comparison |
| Toth, 1973 | Swiss mouse (drinking water) | Hemangiomas and hemangiosarcomas of liver in males and females; alveolar/bronchiolar adenomas and carcinomas in males and females; kidney and liver tumors in males and females; Q1 estimated to be 8.9 (mg/kg/day) |
| Toth, 1977 | Hamster (drinking water) | Hemangiomas and hemangiosarsarcomas in males; colon tumors in males and females |
| Haun, 1984 | F344 rat (inhalation) | Pancreatic islet cell adenomas and carcinomas in males; Q, estimated to be 2.45 (mg/kg/day) 1; pulmonary adenomas and carcinomas in males |
| Haun, 1984 | C57BL/6 mouse (inhalation) | Hemangiomas and hemangiosarcomas in females; liver adenomas in females |
| Uniroyal, 1988e | CD-1 mouse (drinking water) | Blood vessel tumors of the liver in males and females; Q, estimated to be 0.88 (mg/kg/day); alveolar/bronchiolar adenomas in males and females; Q, estimated to be 2.9 (mg/kg/day) |

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TABLE 2

ESTIMATES OF DAMINOZIDE LEVELS IN RAW AND PRODUCED FOODS

| <u>.</u> . | 1.00 |
|------------|----------------------------|
| | 0.50 |
| | 0.40 |
| , | 0.50 |
| | 0.40 |
| | 8.00 # |
| | 4.00 # |
| 30 | 23.7 |
| | 1.5 |
| | 0.0 |
| , | 0.02 |
| | 0.02 |
| 3 3 | 14.5 |
| 3 | 11.3 |
| | 11.3 |
| | 0.80 |
| | 0.80 |
| | 0.80 |
| 3 - | 8.8 |
| | 8.8 |
| | 0.01 |
| | 0.2 |
| | 0.01 |
| | 0.01 |
| | 0.001 |
| | 0.002 |
| 10 | 0.20 |
| | 0.30 # |
| | 0.66 # |
| | 1.10 # |
| 10 | 0.50 # |
| | 10 10 10 10 10 |

- * For commodity items beef, beef byproducts, milk, poultry and eggs, the residue values were extrapolated from feeding studies.
- # Residue levels for dried apples includes a concentration factor of 8. For processed tomato products, the average residue of 0.2 ppm was multiplied by the following concentration factors to derive the value used in calculating exposure: 1.5 for tomato juice, 3.3 for tomato puree, 5.4 for tomato paste, and 2.5 for catsup.

TABLE 3

ESTIMATES OF UDMH LEVELS IN RAW AND PRODUCED FOODS

| COMMODITY | PERCENT OF | NUEDICE |
|-----------------------|--------------|----------------|
| | CROP TREATED | AVERAGE, |
| | CROP IREATED | ppb UDMH * |
| | | |
| Apples | | 2.6 |
| Apple sauce (-baby) | | 33.3 |
| " (-adult) | | 14.0 |
| Apple juice (-baby) | | 44.0 |
| " (-adult) | | 23.9 |
| Dried raw apples | | 20.8 # |
| Dried cooked apples | | 352.0 # |
| Cherries, sweet and s | sour 30 | 18.6 |
| Cherry filling (and j | juice) | 108.1 |
| Grapes | • | 0.0 |
| Grape juice | | 1.5 |
| Grape preserves | | 1.5 |
| Nectarines | 3 | 25.0 |
| Peaches | 3 | 21.3 |
| Peaches, canned | • | 21.3 |
| Peanuts | | 24.9 |
| Peanut butter | | 24.9 |
| Peanut oil | | 24.9 |
| Pears | 3 | 11.9 |
| Pears, canned | ~ | 11.9 |
| Beef meat: | | 2.0 |
| " kidney | | 2.0 |
| " fat. | | 2.0 |
| " milk | | 2.0 |
| Poultry meat | | 0.5 |
| " eggs | | 0.5 |
| Tomatoes, whole | 10 | 1.6 |
| Tomato juice | 10 | 2.4 # |
| Tomato puree | 10 | 5.3 # |
| Tomato paste | 10 | 8.6 # |
| Catsup | 10 | 4.0 # |
| | 20 | च• ∨ ्म |
| | | |

For beef, beef byproducts, milk, poultry and eggs, the residue values were extrapolated from feeding studies.

[#] Residue levels for dried apples includes a concentration factor of 8. For processed tomato products, the average residue of 1.6 ppb was multiplied by the following concentration factors to derive the value used in estimating exposure: 1.5 for tomato juice, 3.3 for tomato puree, 5.4 for tomato paste, and 2.5 for catsup.

TABLE 4

ESTIMATES OF DAMINOZIDE DIETARY EXPOSURE FOR THE U.S. POPULATION *

| | AVERAGE | RESIDUE | • |
|---------------------|---------------------|---------------|--------------|
| | DAILY | LEVELS | |
| : | CONSUMPTION | (in ppm | EXPOSURE |
| COMMODITY | (g food/kg bwt/day) | or mg/kg) (mc | dam./kg/day) |
| Apples, fresh | 0.3074 | 1.00 | 0.000307 |
| Apples, cooked: | | | |
| fresh and juice | 0.2004 | 0.50 | 0.001000 |
| Dried raw apples | 0.0001 | 8.00 | 0.000001 # |
| Dried cooked apples | 0.0001 | 4.00 | 0.0000004 # |
| Apple juice, raw | 0.1709 | 0.50 | 0.000085 |
| Cherries, raw fresh | 9 | | |
| and raw juice | 0.0105 | 7.11 | 0.000075 |
| Cherries, cooked: | | | |
| fresh and juice | 0.0251 | 1.50 | 0.000038 |
| Eggs | 0.5803 | 0.002 | 0.000001 |
| Grapes | 0.0438 | 0.02 | 0.000001 |
| Grape juice | 0.0901 | 0.02 | 0.000002 |
| Wine and sherry | 0.0842 | 0.02 | 0.000002 |
| Nectarines | 0.0130 | 0.45 | 0.000006 |
| Peaches | 0.2154 | 0.34 | 0.000073 |
| Peanuts, raw, | | | |
| cooked, and oil | 0.0748 | 0.80 | 0.000060 |
| Pears | 0.1225 | 0.26 | 0.000032 |
| Meat | 2.2318 | 0.20 | 0.000446 |
| Milk | 1.3705 | 0.01 | 0.000014 |
| Tomatoes, whole | 0.4920 | 0.20 | 0.000098 |
| Tomato juice | 0.0551 | 0.30 | 0.000017 # |
| Tomato puree | 0.1702 | 0.66 | 0.000112 # |
| Tomato paste | 0.0395 | 1.10 | 0.000043 # |
| Catsup | 0.0420 | 0.50 | 0.000021 # |
| TOTAL | | | 0.000951 |
| ***** | | | or |
| | | | O. , |

or 9.5 x 10⁻⁴ mg/kg/day +

For commodity items meat, milk, and eggs, the residue values were extrapolated from feeding studies data.

[#] Residue levels for dried apples includes a concentration factor of 8.
For processed tomato products, average residue of 0.2 ppm was
multiplied by the following concentration factors: 1.5 for tomato
juice, 3.3 for tomato puree, 5.4 for tomato paste, and 2.5 for catsup.

+ 1 percent of exposure (0.95 x 10⁻⁵ mg/kg/day) used to estimate UDMH
contribution from metabolic conversion of daminozide to UDMH when
estimating risk in Table 16.

TABLE 5

ESTIMATES OF UDMH DIETARY EXPOSURE FOR THE U.S. POPULATION *

| MODITY | AVERAGE DAILY CONSUMPTION (q food/kg bwt/day) | RESIDUE LEVELS (in ppb or ug/kg)(ug | EXPOSURE |
|---|---|--|------------------------|
| MMODIII | (d 100d/kg bwc/day) | OI ady kay tad | ODMIN/ KG/ Gay I |
| les, fresh | 0.3074 | 2.6 | 0.000799 |
| ples, cooked: | | | |
| fresh and juice | 0.2004 | 44.0 | 0.008818 |
| ed raw apples | 0.0001 | 20.8 | 0.000002 # |
| ed cooked apples | 0.0001 | 352.0 | 0.000035 # |
| ple juice, raw | 0.1709 | 33.3 | 0.005691 |
| erries, raw fresh | | | |
| and raw juice | 0.0105 | 5.6 | 0.000059 |
| erries, cooked: | | | |
| fresh and juice | 0.0251 | 108.1 | 0.002713 |
| ģs | 0.5803 | 0.5 | 0.000290 |
| āpes | 0.0438 | 0.0 | 0.000000 |
| ape juice | 0.0901 | 1.5 | 0.000135 |
| he and sherry | 0.0842 | 1.5 | 0.000126 |
| ctarines - | 0.0130 | 0.8 | 0.000010 |
| aches | 0.2154 | 0.6 | 0.000129 |
| aches anuts, raw, | | | • |
| cooked and oil | 0.0748 | 24.9 | 0.001863 |
| ars at lk matoes, whole mato juice mato puree | 0.1225 | 0.4 | 0.000049 |
| at | 2.2318 | 2.0 | 0.004464 |
| lk | 1.3705 | 2.0 | 0.021068 |
| matoes, whole | 0.4920 | 1.6 | 0.000787 |
| mato juice | 0.0551 | 2.4 | 0.000132 # |
| mato puree | 0.1702 | 5.3 | 0.000902 # |
| mato paste | 0.0395 | 8.6 | 0.000340 # |
| mato paste tsup | 0.0420 | 4.0 | 0.000168 # |
| TAL | | | 0.000047 |
| , | | | or |
| | | | $4.7 \times 10^{-5} +$ |
| | | | mg/kg/day |

For commodity items meat, milk, and eggs, the residue values were extrapolated from feeding studies data. All beef, beef byproducts and poultry were combined under "meat" in this table.

Residue levels for dried apples includes a concentration factor of 8.

For processed tomato products, average residue of 1.6 was multiplied by the following concentration factors: 1.5 for tomato juice, 3.3 for tomato puree, 5.4 for tomato paste, and 2.5 for catsup.

1 percent of daminozide exposure (0.95 x 10 mg/kg/day) added to

total UDMH dietary exposure in Table 16 used to estimate 1 percent conversion of daminozide in the gut.

TABLE 6

TAS ESTIMATES OF AVERAGE DAILY EXPOSURE TO DAMINOZIDE FOR SELECTED AGE SUBSETS

| Subset (Age and Other) | Exposure (mg/kg/day) |
|--------------------------------------|----------------------|
| AVERAGE (U.S. POPULATION) | 0.000951 |
| Nursing infants (<1 year old) | 0.003396 |
| Non-nursing infants (<1 year old) | 0.005427 |
| Children (1 - 6 years old) | 0.002786 |
| Children (7 - 12 years old) | 0.001514 |
| Males (13 - 19 years old) | 0.000730 |
| Females (13 - 19 years, not pregnant | |
| or nursing) | 0.000662 |
| Females (13 + years, pregnant) | 0.000692 |
| Females (13 + years, nursing) | 0.000824 |
| Females (20 + years, not pregnant | |
| or nursing) | 0.000575 |
| Males (20 + years old) | 0.000523 |

ESTIMATES OF UDMH DIETARY RISK FOR THE U.S. POPULATION

(interim $Q_1^* = 0.88 \text{ mg/kg/day}$)

| | 1 | Dietary Exposure | Dietary |
|------------|---|------------------|---|
| Commodity | 1 | (ug/kg/day) | <u>Risk</u> * |
| Milk | | 0.021068 | 1.8 x 10 ⁻⁵ |
| Apples | • | 0.015331 | 1.4×10^{-5} |
| Red meat: | | 0.004464 | 3.9×10^{-6} |
| Cherries | | 0.002772 | 2.4×10^{-6} |
| Peanuts | | 0.001863 | 1.6×10^{-6} |
| Eggs | | 0.000290 | 2.5×10^{-7} |
| Grapes | | 0.000261 | 2.3×10^{-7} |
| Poultry | | 0.000252 | 2.2 x 10 ⁻⁷ |
| Tomatoes | | 0.000234-0.00234 | $2.1 \times 10^{-7} - 2.1 \times 10^{-6}$ |
| Peaches | | 0.000129 | 1.1×10^{-7} |
| Pears | | 0.000049 | 4.3×10^{-8} |
| Nectarines | | 0.000010 | 8.8 x 10 ⁻⁹ |

TOTALS

0.046715

4.1 X 10⁻⁵

+[0.009500 estimated metabolic UDMH from daminozide] 0.84 X 10⁻⁵

4.9 X 10⁻⁵

* Refer to II.C.3.b. "Uncertainties that Could Overestimate the Risk (2-3)".

The following Table 4 presents the average daily total dietary exposure to daminozide and UDMH, respectively, for various age groups to demonstrate the differences in dietary exposure.

TAS ESTIMATES OF AVERAGE DAILY EXPOSURE TO UDMH FOR SELECTED AGE SUBSETS

| Subset (Age and Other) | Exposure (mg/kg/day) |
|--------------------------------------|----------------------|
| AVERAGE (U.S. POPULATION) | 0.000047 |
| Nursing infants (<1 year old) | 0.000229 |
| Non-nursing infants (<1 year old) | 0.000410 |
| Children (1 - 6 years old) | 0.000138 |
| Children (7 - 12 years old) | 0.000071 |
| Males (13 - 19 years old) | 0.000042 |
| Females (13 - 19 years, not pregnant | |
| or nursing) | 0.000034 |
| Females (13 + years, pregnant) | 0.000027 |
| Females (13 + years, nursing) | 0.000037 |
| Females (20 + years, not pregnant | |
| or nursing) | 0.000023 |
| Males (20 + years old) | 0.000025 |

Table describes the average incremental risk for individuals who belong to any of the three subgroups for which dietary exposure was estimated. Annual risk was calculated by multiplying the average residue contribution for each subgroup by the interim cancer potency factor $(Q*1 = 0.88 \text{ (mg/kg/day)}^{-1})$ and then dividing the calculated risk by 70 lifetime years.

TO SELECTED AGE SUBSETS AND THE GENERAL POPULATION FROM ONE YEAR EXPOSURE TO UDMH

| A service of the serv | | |
|--|------------------------------------|--|
| Subset (Age and Other) | Dietary Exposure (mg/kg/day) | Annual Risk |
| Nursing infants (<1 year old) Non-mursing infants (<1 year old) Children (1 - 6 years old) | 0.000229 0.000410 0.000138 | 2.9 x 10 ⁻⁶ 5.2 x 10 ⁻⁶ 1.7 x 10 ⁻⁶ |
| AVERAGE LIFETIME RISK TO THE GENERAL POPULATION FROM ONE YEAR EXPOSURE | 0.000047 | 5.9 x 10 ⁻⁷ |

2. Nondietary risks

The exposure estimates discussed in section II.B.2. are used as a basis for estimating non-dietary carcinogenic risk. The Agency assumed that the cancer potency factor for the dermal route of exposure is equivalent to that for the dietary route (0.88) and that the length of lifetime exposure is 35 years worked/70 years lived. To calculate non-dietary carcinogenic risk from exposure to UDMH, the Agency used the following equation:

UDMH risk = UDMH exposure x 35/70 x Q_1^* (0.88 (mg/kg/day)¹)

Based on this calculation, the carcinogenic risks from worker exposure to UDMH is tabulated in Table 18.

Birnbaum

EPA Moves to Reassess the Risk of Dioxin

Urged on by the scientific community, EPA is developing a new model for estimating dioxin's risk

GALVANIZED BY THE RESULTS OF A RECENT scientific meeting on dioxin's molecular actions, Environmental Protection Agency (EPA) administrator William K. Reilly has launched a major new effort to reassess the toxicity of this ubiquitous—and infamous—chemical.

Responding to criticism that the model EPA now uses to assess dioxin's risk is obsolete, Reilly has asked agency scientists to come up with a new "biologically based" model that will draw on an emerging understanding of the first steps that take place as dioxin enters a cell (for example, see pages 924 and 954). Reilly and others call the new effort "precedent-setting" not only for how the agency regulates carcinogens but also for EPA's quick response to new scientific developments—not its strong suit in the past.

Until now, EPA has gauged the risk of dioxin exposure by using the same model it applies to most carcinogens: the linear multistage model, which assumes that risk rises in proportion to close. Agency officials have long viewed the model as a "default"—one adopted for lack of a real understanding of how carcinogens work—and their intent was always to replace it with something more realistic once mechanisms were understood. But so far, they say, such evidence has been lacking. Now it may at last be in hand, at least for dioxin and perhaps a handful of other chemicals that behave similarly.

The turning point came in an 8 March briefing for Reilly and his top deputies given by three agency scientists: William Farland and Peter Preuss, both at EPA headquarters in Washington, D.C., and Linda Birnbaum of EPA's Health Effects Research Laboratory in North Carolina. Part of the briefing was devoted to recent epidemiologic studies, including the new one by Marilyn Fingerhut of the National Institute for Occupational Safety and Health (NIOSH), which found perhaps the strongest link yet between high doses of dioxin and human cancer (see Science, 8 February, page 625). The EPA scientists also discussed a reanalysis of data from a 1.976 study of cancer in dioxin-exposed rats that figured heavily in EPA's original risk assessment. After reexamining the original slides of liver tissue, investigators have concluded that the animals developed fewer tumors than was originally believed.

But it was Birnbaum and Farland's description of a meeting last November at the Banbury Center at Cold Spring Harbor

Laboratory that Reilly says made the most compelling case for change. At that meeting a group of dioxin experts agreed that before dioxin can cause any of the ill effects it has been linked to—cancer, immune system suppression, chloracne, and birth defects-one "necessarv but not sufficient" event must occur: the compound must bind to and activate a receptor, known as the aryl hydrocarbon or AH receptor (see Science, 8 February, p. 625). After that, the dioxin-receptor complex is transported to the nucleus, where it binds to specific sequences of

DNA and turns genes on and off, thereby causing its myriad effects. It had long been known that dioxin binds to a receptor, but before the Banbury meeting it had been unclear whether all of dioxin's effects or just some were mediated this way.

The Banbury group also agreed that dioxin has to occupy a certain number of AH receptors on a cell before any biological response can ensue. The result is a practical "threshold" for dioxin exposure, below which no toxic effects occur. That conclusion flies in the face of the linear model's underlying assumption: that the risk of harmful effects begins with exposure to a single molecule and increases from there. Faced with this new picture of dioxin's action, the Banbury participants urged EPA to develop a new, receptor-based model for dioxin risk assessment.

Reilly bit. He has now asked scientists in EPA's Office of Research and Development, in collaboration with academic researchers around the country, to come up with just such a model. The goal, explains Michael Gallo of the Robert Wood Johnson Medical School, one of the organizers of the Banbury

meeting who is now working with EPA, is to pinpoint the threshold or "safe" dose below which none of dioxin's ill effects should occur.

In building the model, Gallo and his EPA colleagues hope to draw on work on the dioxin receptor now under way in a number of labs around the country. In this issue of *Science*, for example, a group headed by Oliver Hankinson of the University of California at Los Angeles reports on the cloning of a protein that is necessary for the receptor to function. Various roles have been proposed for the new protein; one intriguing possibility is that it is part of the receptor itself. The dioxin receptor thus might contain

at least two proteins, one that binds to dioxin (and presumably whatever natural molecule dioxin mimics) and another that binds to DNA. "Boy, is that exciting," says Gallo, who adds that the new findings will feed directly into the model.

Until the model is complete, no one can say for sure whether it will show dioxin to be more or less risky than EPA now calculates, though Gallo and others speculate that it will turn out to be less risky. One of the major questions is how close the presumed "safe" dose is to the background levels of dioxin to which the general popula-

tion is exposed. If background exposure is already near the "safe" dose, then there may not be much room for additional exposure.

Those background levels are largely unknown, so Reilly has added that question to the EPA scientists' assignment. Over the next year Birnbaum and other EPA scientists, in collaboration with researchers from NIOSH, the Centers for Disease Control, and the Air Force, hope to get a fix on blood levels of dioxin and the handful of polychlorinated biphenyls that behave similarly and thus could increase its risk. Meanwhile, other researchers will be studying the sources and routes of dioxin exposure—most of which are dietary—and how it is passed up the food chain.

Reilly wants the new model and related work complete within a year, at which time the results will go on to EPA's Scientific Advisory Board (SAB) for peer review. Three years ago, the SAB sent EPA scientists back to the drawing board when they tried to revise the dioxin standard, saying the science wasn't sound enough. Birnbaum and other EPA researchers predict a different outcome this time.

LESLIE ROBERTS



Key mover. Linda Birnbaum had been urging EPA to change how it does dioxin risk assessment.

US government orders new look at dipxin 0 4 1991

DR. TERRI DAMSTRA

The Environmental Protection Agency is evaluating data from the past decade that suggest dioxin's toxicity may be overestimated. A risk assessment model based on biological mechanism is being drawn up.

States as the most toxic chemical known to man. As a component of the infamous Agent Orange that the US used to defoliate the jungles of Vietnam, after the war dioxin was blamed for cancer in servicemen who saw duty there. Although compensation was finally offered, neither solid epidemiological nor biological proof of cause and effect has been conclusively demonstrated.

When a chemical plant exploded at Seveso, Italy in 1976, spewing dioxincontaminated agents into the air, it was feared (and assumed) that the exposed citizens of the town would experience increased cases of cancer and/or birth defects. In fact, severe chlorachne was reported but, fortunately, more life-threatening diseases were not.

When, in 1982, the soil in the small town of Times Beach, Missouri was found to be contaminated by dioxin at levels around I part per million, US government officials closed the town down permanently and evacuated its 2,000 residents to safer ground across the river. Nearly a decade later, clean-up work is still going on. Someday, when the soil is incinerated and the buildings are all torn down, Times Beach may be turned into a park.

Over the years, hundreds of millions of dollars have been spent getting rid of dioxin, which has earned its reputation as a killer because it is highly carcinogenic in guinea pigs and and causes birth defects in mice exposed to small concentrations of 2,3,7,8-tetrachlorodibenzo-p-dioxin or TCDD.

Now, into this politically charged arena comes William K. Reilly, the head of the US Environmental Protection Agency, saying that dioxin may not be so exceptionally toxic after all. During the past several years, data in humans has accumulated that question the validity of extrapolating TCDD data from guinea pigs to man. Reilly has called for a total reevaluation of dioxin in all of its many chemical forms (there are 75 or so).

It takes a brave man to put scientific evidence ahead of deeply ingrained public opinion. The last time a federal official suggested that dioxin standards could be relaxed was in 1989 when Vernon Houck of the Centers for Disease Control in Atlanta advised the state of Georgia about water standards. Shortly thereafter, he was subjected to a congressional inquiry into his possible bias toward the paper indus-

Dioxin is widely thought of in the United | try which puts dioxin-contaminated | wastes into streams after bleaching pulp. Houck stood his ground, testifying that "new information indicates that we should be less concerned than we once were."

In March of this year, Reilly and other top EPA officials received a briefing on dioxin that Reilly credits for his change of mind. First, his advisers reported an unusual consensus from a recent dioxin conference at the Banbury Center at Cold Spring Harbor, New York. Researchers agreed that the toxicity of TCDD depends upon its binding with the aromatic hydrocarbon receptor, or Ah. Most to the point, they agreed that receptor binding mediates TCDD toxicity in virtually every test system studied, and that receptor binding needs to occur in thousands of cells, though the dividing line between safe and toxic concentrations is not known.

Nevertheless, this observation leads directly to Reilly's conclusion that "work should begin on a new biologically-based model for assessing the toxicity of dioxin." Until now, the Environmental Protection Agency has relied on the standard linear multistage model that predicts no threshold of safety. Based on this model, US standards for exposure to 'background' levels of dioxin that is in the environment are stringent: .006 picograms per kg body weight per day for intake from food or water, for instance. Interestingly, Canadian and European scientists generally have not accepted the US position that dioxin is the most toxic chemical around. Conservative estimates put a safe dioxin intake at 1 picogram per kg per day, while more liberal standards go as high as 10 picograms per kg. Although no changes in US regulations have been put forward, it is likely that the US will move in the direction of its neighbours abroad.

A second bit of data that figured in Reilly's request for a new look at dioxin comes from a large epidemiological study reported in the 24 January issue of The New England Journal of Medicine. Researchers at the US National Institute for Occupational Safety and Health in Cincinnati, Ohio, conducted a retrospective mortality study of 5,172 workers at 12 chemical plants that produce agents in which TCDD is a contaminant. Their conclusions: "Mortality from several cancers previously associated with TCDD (stomach, liver, and nasal cancers, Hodgkin's disease and non-Hodgkin's lymphoma) was not significantly elevated in this cohort. Mortality from soft-tissue sarcoma was increased but not significantly.'

Government scientists, working with colleagues in universities, have been asked not only to develop a biologically based or receptor model, but also to construct a plan for evaluating the new epidemiological data so that any new standard-setting regulations encompass the new data as a whole. March of 1992 is the target date for completion of the work.

Environmental Protection Agency scientists seem to be fully aware that they are entering dangerous territory. Even though data may exonerate dioxin somewhat, it remains a toxic contaminant of the environment that has no compensating benefit. Furthermore, a reassessment of dioxin has obvious implications for related polychlorinated biphenyls. Ultimately, it could lead to a biologically based model for any agent or group of agents for which toxicity is understood at a mechanistic level.

That the government must proceed carefully, and openly, is vital. Reilly has promised independent scientific review, which is certain to be subject to harsh scrutiny by groups committed to the view that the only acceptable risk is no risk at all. Over the years, this has become the unstated goal of many groups in the United States, but with science's ability to measure chemicals at ever smaller concentrations, it becomes crucial to rank toxic compounds in some sensible order of hazard. As Reilly has noted, "There simply are more anxieties than we can possibly create laws to alleviate, and far more risks than resources to eliminate them.

There is no doubt that a decision to declare dioxin less hazardous will be painful, particularly to the people at Times Beach and elsewhere whose lives have been so totally disrupted. At the time steps were taken to evacuate the town, the decision was entirely in keeping with scientific data available. Human data were scarce. It was thought prudent to rely on animal data and they made a strong case for judging dioxin to be unusually toxic. Although researchers may be comfortable with the idea that new judgements should correctly follow new data, it remains a difficult concept for the

Nevertheless, it is time to set priorities, even if it is politically treacherous.

Barbara J. Culliton

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Dioxin Toxicity: New Studies Prompt Debate, Regulatory Action

New data on dioxin's effect on humans, a clearer picture of the cellular events it precipitates, and new animal toxicity studies may provide EPA with a firmer basis for regulation

David J. Hanson, C&EN Washington

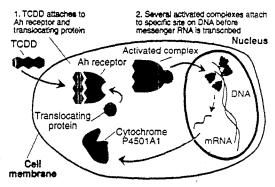
Of all the chemicals that have been tossed into the caldron of public anxiety, 2,3,7,8-tetrachlorodibenzo-p-dioxin, TCDD, has achieved the most notoriety and evoked the greatest fears for the longest period of time. Beginning with herbicide use during the Vietnam War, propelled by Love Canal and Times Beach, and sustained by reports of contamination from city incinerators and paper mills, TCDD essentially defines chemical contamination for most people.

TCDD was first implicated as the culprit responsible for illnesses among chemical industry workers who produced 2,4,5-trichlorophenol. However, the chemical was thought to be only of industrial concern until the mid-1970s. In 1976, an explosion at a chemical plant spread from 1 to 4 lb of TCDD over the residents of the town of Seveso, Italy. High TCDD levels were recorded in people from the area. Shortly afterward, many Vietnam veterans began wondering if their range of illnesses could have been caused by exposure to the herbicide agent orange which was known to be contaminated with TCDD.

When TCDD was found to be part of the highly reported and emotionally charged hazardous-waste leakage that resulted in evacuation of the community of Love Canal, Niagara Falls, N.Y., in 1980, and evacuation and purchase by the federal government of the entire town of Times Beach, Mo., in 1983, it became firmly impressed in people's minds that here was a chemical problem of elephantine proportions. But just as the four blind men each described an elephant differently because they were each touching different parts of the animal, so different scientists, government officials, corporations, and environmental activist groups describe the hazards of TCDD differently. It is only recently that a clearer picture of this creature has emerged, and while it may not be the mammoth once believed, it is no mouse either.

Several events have come together over past months that have helped focus the picture. One is a symposium

Receptor-mediated TCDD action requires several steps



Messenger RNA carries code for cytochrome P4501A1 or other enzymes

In the cell, 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) binds strongly to a soluble intracellular protein designated the Ah (for aryl hydrocarbon) receptor, which then binds to a translocating protein that carries the "activated complex" into the cell nucleus. Several activated complexes bind to specific DNA sequences, distorting the DNA chain. Ensuing events lead to transcription of messenger RNA that codes for cytochrome P4501A1 or other enzymes

held at the Banbury Center at Cold Spring Harbor Laboratory, New York, in October that took a critical look at the state of the molecular science of TCDD. The conclusions reached there are extending far beyond research laboratories. Another is the release of significant epidemiological research data involving people exposed to TCDD aimed at determining whether or not they are suffering illnesses as a result. The Environmental Protection Agency, some say in response to these events. has

undertaken an important review of TCDD toxicity that may lead it to change its policies on carcinogenicity.

Much of TCDD's dreadful image stems from its label as "the most toxic synthetic chemical known to man." It is widely conceded that this label is attributable to early research that found that as little as 0.6 µg per kg body weight could kill 50% of guinea pigs exposed to TCDD. Research by Dow Chemical scientists in 1978 found that the chemical was also a potent carcinogen in rats. These facts, repeated in virtually all newspaper and television reports about TCDD, made the chemical the most feared of all contaminants.

Subsequent decisions to lower TCDD concentration in the environment led to the banning of products such as 2,4,5-trichlorophenoxyacetic acid, a herbicide contaminated with TCDD. Production of other products, especially those that used 2,4,5-trichlorophenol as a precursor, was stopped. When it was discovered that municipal and hazardous-waste incinerators were large sources of TCDD in the environment, new controls were implemented to limit TCDD emissions. Use of leaded gasolines was also found to be a prime source of environmental TCDD, and EPA's phaseout of leaded gasoline has also resulted in reduced emissions.

Based on its current risk assessment model, EPA has calculated that the tolerable daily intake of TCDD for humans is 0.006 picograms per kg body weight per day. This level would supposedly result in a one in 1 million chance of excess cancer from TCDD. But this level is far, far below the 1 to 3 picograms per kg body weight per day that people are estimated to be actually ingesting. Other nations, using different risk assessment models, have calculated the tolerable intake level much higher. Germany uses 1 picogram, the Netherlands 4, and Canada and the World Health Organization use 10 picograms per kg body weight per day.

Because health problems associated with TCDD exposure first came to light as the result of chemical industry accidents in the 1950s, the industry has always been a target of blame for environmental contamination. Dow Chemical, Monsanto, and six other chemical companies that made agent orange for the federal government during the Vietnam War were the defendants in a major lawsuit that was settled when the companies

agreed to pay \$180 million to veterans claiming illnesses resulting from exposure to the herbicide. TCDD has subsequently been at the root of thousands of injury lawsuits, including cases filed by people who lived at Times Beach and Love Canal.

A significant decision was handed down this summer when the Illinois Appellate Court of the 5th District overturned a \$16.25 million punitive damage verdict against Monsanto (C&EN, June 24, page 6). The jurors had found no injuries among people claiming to have been injured by dioxin exposure following a train accident,

| but decided to punish Monsanto anyway. The appeals |
|--|
| court judges ruled that if there are no injuries, r ve |
| damages cannot be exacted. A request to have an- |
| peal reheard was also rejected. |

Some attorneys specializing in personal injury cases believe this decision may be a turning point for TCDD and other chemical injury cases. David G. Owen, law professor at the University of South Carolina, for instance, says: "The decision may stand as a declaration of judicial intolerance to the use of courtrooms as arenas for subjecting U.S. industry to political and ideological persecution."

David Snively, litigation counsel for Monsanto, has already seen an actual drop-off in dioxin litigation. The company ceased making chlorinated phenols a decade ago, and Snively says about the only relationship Monsanto now has with TCDD is some research. "There has been a fall-off in litigation involving Monsanto, and we have no active lawsuits," he says. He has noticed that new lawsuits seem to be cropping up in the paper and pulp industry.

The paper industry was surprised in 1985, when TCDD was discovered in the effluent and sludge from paper mills. It was found that chlorine bleaching of the pulp caused TCDD formation. Claims soon arose that TCDD was leaching into children's milk cartons, and EPA found itself faced with a lawsuit brought by the National Wildlife Federation and the Environmental Defense Fund demanding regulation of TCDD in the mill effluent.

Although concerns about human health h. .rds from paper products have subsided, the environmental concerns have spurred paper manufacturers to treat effluents to reduce TCDD and to look into process changes to decrease TCDD production. The industry uses about 14% of all chlorine produced in the U.S. and concentrations of TCDD in the effluents are in the partsper-quadrillion range. The Chlorine Institute, which represents the chlor-alkali industry, is very worried about this problem, but maintains that the parts petrillion and lower concentrations of dioxins and furan generated by papermaking do not pose a health or en vironmental threat.

However, the Chlorine Institute was one of the spon

sors of the Banbury Center meeting. The conference, which brought together 38 invited scientists from the U.S. and Europe, was actually the second meeting held to discuss TCDD; the first was in 1985. In addition to the Chlorine Institute, the meeting was cosponsored by EPA and FDA. All scientific aspects of the issue were laid out at the conference, and by the end, there was some general agreement on several issues.

Michael A. Gallo, associa an of research at the Robert Lod Johnson Medical School in New Jersey, was one of the conference organizers. "We met for four days

TCDD toxicity varies greatly among species

| Species | LD _{se} (μg per kg) |
|------------|------------------------------|
| Guinea pig | 0.6-2.5 |
| Mesic | 4 |
| Rat | 22-320 |
| Monkey | <70 |
| Rabbit | 115-275 |
| Mouse | 114-280 |
| Dog | >100-<3000 |
| Hameter | 1150-5000 |

and we reviewed all the science, and we reviewed a lot of the mathematical and biological models that went into it. We came away with the idea that the primary events in and around dioxin were related to this thing we call the Ah receptor." Gallo says the meeting did clarify the scientific issues in that "it helped focus the thought patterns of where a lot of people want to go over the next year, and I think it focused where [EPA Administrator] Bill Reilly and EPA have to put their energies."

Overshadowing everybody's concern over TCDD is that, despite the compound's obvious toxicity to animals, no clear-cut human health problems were associated with TCDD exposure, even though a number of human exposure incidences were known. Epidemiologic studies undertaken to identify any major health problems always

had so many shortcomings that researchers could not say whether TCDD had an effect or not. This year two studies have brought the answer closer.

The Air Force Ranch Hand study, begun in 1978, is the oldest study of people heavily exposed to TCDD and the most controversial. An ongoing study, it continues to draw severe criticism. Study participants are members of Operation Ranch Hand, the group that actually handled and sprayed agent orange over the fields and forests in Vietnam from 1962 to 1971. Agent orange was used to defoliate forests and kill some crops in Vietnam for the protection of U.S. forces. It was a 50-50 combination of the herbicides 2,4,5-T and 2,4-D and was contaminated with about 2 ppm or less of TCDD. The original study involved 1242 Rand Hand personnel, although the actual number of participants varies somewhat from examination to examination.

The strongest critic of the Ranch Hand studies has been the American Legion, which represents U.S. veterans who served in Vietnam. The American Legion says the Ranch Hand studies are not designed well enough to see excess diseases because of too few participants and that the classification for exposure was improperly done. It further charges that the Air Force has actually suppressed adverse health effects findings. Despite the Air Force's claims of no significant illness such as cancer or reproductive effects, the legion, with backing from some researchers it has supported to do its own reviews, believes the Ranch Hand personnel have suffered from TCDD exposure.

No one has doubted that those in the Ranch Hand study were exposed to TCDD. In the Air Force's latest report, issued in March, the blood levels of TCDD were measured in 866 Ranch Hand veterans and 804 comparison veterans for the first time, and those levels were correlated to any health effect they could find. Values for TCDD in blood serum ranged from 0 to 618 ppt in



Houk: improve risk assessments

Ranch Hand personnel, but the median value was 12.8. Median value of the comparison group was 4.2. Aside from some other, very minor correlations, the report found a significant increase in body fat and diabetes that correlated with TCDD concentration.

This was a surprise, according to William H. Wolfe, chief of the epidemiology research division of Armstrong Laboratory at Brooks Air Force Base in Texas, which is the lab responsible for Operation Ranch Hand. "This obviously needs a closer look." Wolfe says. "We are doing another examination of the same group starting early next year. We are changing and extending our physical examination tests to look critically at the diabetes and to get more answers." Wolfe adds that this finding, while serious, did not get much attention perhaps because

"it is not one of the diseases that people had a vested interest in." The American Legion criticisms of the March Ranch Hand report did not even mention the diabetes finding.

Wolfe admits that some of the criticisms of the Ranch Hand study are valid. The small sample size is a problem for identifying increases in diseases like rare cancers. "These limitations were all laid out at the beginning," Wolfe says; "we just got all the Ranch Handers there were." Statistically, he says, "the study has only a 50% ability to detect a doubling of rare cancers like soft tissue sarcoma. And that's too low." For detecting a rise in all cancers, the odds are better. "If we take all cancers together, we have a 90% chance of detecting a 50% increase," he says.

The complaints that data have been deliberately withheld are groundless, Wolf says. He points out that all the data go through a review committee that makes recommendations for additions or changes, which are taken care of before the report goes to the Surgeon General. Given the advisory committee oversight, Wolfe does not see how data could be left out, especially since Sen. Tom Daschle (D.-S.D.), concerned that the Ranch Hand study might be getting inappropriate advice, changed the board composition so that 30% of its members were nominated by veterans groups.

One of the most emotional issues of TCDD has followed in the wake of the Ranch Hand study. That is, whether other soldiers who served in Vietnam suffered from exposure to agent orange and the dioxin that contaminated it. Study after study by the government have shown that men and women serving in Vietnam were not exposed to high levels of TCDD. The Centers for Disease Control tried more than once to find a correlation between Vietnam service and health problems or blood serum dioxin concentrations and could not find one. The Department of Veterans Affairs also has stud-

News Focus

ied veterans and concludes that agent orange caused no health problems.

The most recent report came from Han K. Kang, head of the Office of Environmental Epidemiology at DVA. Published in March, Kang's study measured blood serum TCDD levels in 36 veterans who, from as best as could be determined from records of agent orange spraying and troop positions, might have been exposed to the herbicide. "We tried to come up with an exposure assessment based on this," Kang says. "We couldn't find any increased exposure. The difference between their body burdens of TCDD was not significant" compared with the control group. Kang says DVA is finished with efforts to determine TCDD levels in Vietnam veterans. "We have done all we can in dealing with the veterans," he

says. "We are satisfied with the conclusion that there is no significant elevation in TCDD levels."

One striking finding by Kang is that the body burden of TCDD in the population appears to be falling. The samples he measured were collected in the early 1970s by the National Human Adipose Tissue Monitoring Program. Kang reported mean background levels of about 12 ppt for these samples. More recent work, such as that done by CDC, found background levels of TCDD at 5 to 7 ppt. "We are speculating that the environmental TCDD levels are going down, for whatever reason. Other countries, like Sweden, have also reported that organic compounds, including TCDD, are declining," Kang says.

Another reason DVA does not feel it needs to do more studies is a change in administrative policy made in 1990 by Secretary Edward J. Derwinski. In response to a lawsuit filed in California, the department has begun offering compensation to Vietnam veterans who suffer from diseases thought to be caused by agent orange exposure, even though no such link has ever been proven. The diseases currently accepted are soft tissue sarcoma, non-Hodgkins lymphoma, and a nerve problem called peripheral neuropathy.

The epidemiology study likely to carry the most weight in the TCDD discussion was published in January by Marilyn Fingerhut and her colleagues at the National Institute for Occupational Safety & Health. Her retrospective cohort study of cancer mortality included 5172 chemical plant workers from 12 companies who had worked in areas making products that were contaminated with TCDD. Generally they worked at plants that produced or used 2,4,5-trichlorophenol. Of these workers, 1052 had died, and the study is based on data on their cause of death. Fingerhut also had blood samples taken from 253 workers from two plants for measuring

TCDD has several toxic effects

Death

Wasting syndrome

Thymic atrophy

Splenic atrophy

Teeticular atrophy

Liver enlargament, fatty deposits, necrosis Hyperplasta: gastric mucosa, urinary tract, bile duct

Squamous metaplatita: melbornian giands, ceruminous giands

Chloracne: hyperplanta, hyperkeratosis, altered pigmentation

Teratogenosis

Carcinoganesia

Immunosuppression

Enzyme induction

Biochemical effects

Source: Environmental Protection Agency

serum TCDD levels. The partipants were divided into gro that had less than or more than one year of exposure to TCDDcontaminated materials. A separate analysis was done of individuals who were exposed more than 20 years ago.

John C. Bailar III of McGill University said in an editorial appearing in the same issue of the New England Journal of Medicine as Fingerhut's study was published, "Parties on both sides of the continuing debate about the regulation of dioxin exposure will no doubt cite this work in support of their positions." And he was right.

Among the significant conclusions reached by Fingerhut's group is that, for the group that was exposed to TCDD for longer than a year and with more than 20 years' latency, deaths from cancers of all kinds combined

were 46% higher than for the general population. "This is an unusual finding for chemical workers," Fingerhut explains. "Chemical worker studies to my knowled have not shown that. In the few I'm aware of that seq excess in all cancers, the excess has been accounted for by a single-site cancer, say lung cancer." Because of the problem of multiple exposures to chemicals among plant workers, Fingerhut explains, TCDD cannot unequivocally be said to be the cause for this observation, but "it appears to us that the most likely explanation is the exposure to chemicals contaminated with TCDD."

"We showed in this paper a striking correlation between serum levels of TCDD and duration of exposure," Fingerhut says. Consequently, it will allow followup studies to assume that workers of longer duration will have higher levels of TCDD in their blood. It is also of note that, with one exception, the Fingerhut study did not find excess cancer deaths from any one type of cancer, including non-Hodgkins lymphoma, which in the past has been associated with TCDD exposure. The Fingerhut report is inconclusive on the issue of TCDD's causing soft tissue sarcoma. Some say her finding of three deaths when less than one was predicted proves the connection. Others say the numbers are just too small to be meaningful. "As time goes on, reanalysis of this study group will be more powerful and it may be that the interpretation will become more clear," Fingerhut says.

To Vernon N. Houk, director of the Center for Environmental Health & Injury Control at the Centers for Disease Control, the issue is mostly decided. "I belighted that a conservative interpretation of the Fingerhut st is that if dioxin is a human carcinogen, which I am assuming it is, it is a relatively weak one and is a carcinogen only at extraordinary doses." Houk notes that Fingerhut's study agrees with results from the Ranch Hand

TCDD antiestrogen effect has tumor-fighting potential

After more than 30 years of experience, there is little doubt that 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) is a clangerous chemical to have in the environment. Still, approximately 10 years ago, a few scientists took note of one effect of TCDD in rats and have since been pursuing an interesting and potentially valuable line of research.

As Michael A. Gallo, associate dean for research at the Robert Wood Johnson Medical School in New Jersey, tells it, it all started with a Dow Chemical study by Richard J. Kociba, published about 13 years ago. The study showed an increase in liver cancer in rats exposed to TCDD, "but at the same time there was a remarkable decrease in spontaneous breast tumors and spontaneous uterine tumors," Gallo says. He and others began looking into this effect, wondering if TCDD, which seemed to be reacting with a hormonelike receptor, might be an anliestrogen. If it was, and could somehow be controlled, there was a potential for reducing women's risk of estrogen-dependent breast cancer.

Gallo says early tests in mice confirmed that TCDO did somehow prevent estrogen from doing its job. "One experiment to measure estrogen activity is to inject estrogen into an immature mouse. The uterus will then mature very rapidly. So you end up with an immature animal with a mature uterus. We did it the other way. We injected immature animals with TCDD (an antiestrogen). The untreated mice went on to develop normal uteruses and the animals given TCDD had immature organs." It was clear TCDD was preventing estrogen from acting.

There are two ways this might occur. The first is that the TCDD-receptor complex is actually inducing production of an enzyme that metabolizes estradiol. Gallo says there is some evidence of this, but that it alone is probably not enough to account for TCDD's observed antiestrogenic effects.

Gallo and collaborator Steven H. Safe, of the department of veterinary medicine at Texas A&M University, are working on the assumption that the TCDO receptor is somehow interfering with production of the normal estrogen receptor in cells. "We see changes in the messenger RNA for the estrogen receptors," he says. "It's decreased.

And the actual estrogen receptor protein is decreased after TCDD treatment at very low doses." Safe adds that "TCDD also seems to block other stimulatory agents that make breast cancer cells grow."

A common drug used currently as a palliative breast cancer therapy, tamoxifen, has some side effects and, Gallo says, about 15% of the patients put on the drug become susceptible to tumors again after five or six years. "If we had a drug that didn't allow the estrogen receptors to be synthesized in these cancer victims, we wouldn't have to worry about blocking their action," he explains. Thus, if TCDD does functionally block formation of estrogen receptors, there is clinical potential.

Of course, the toxicity of TCDD is such that it would not be used as a drug. However, Safe says they have aiready synthesized relatively nontoxic TCDD analogs to see if those compounds produce the same responses. "Other dioxins and dibenzofurans that we've made have less toxicity but they still seem to have these potent antiestrogenic effects. Not as potent as TCDD, but still pretty good," Safe says.

study in that persons exposed at moderate levels do not seem to be having excess cancer mortality. He hopes that this, as well as additional research will be used in the future to make better risk assessments. "The federal government has spent more than \$400 million to research this compound, in addition to what the companies have spent. If we don't use that new information to modify or support our views on dioxin, then why did we do it?"

The next body of knowledge coming to bear on TCDD's toxicity will be the result of research on animals and at the molecular level. One of the most significant realizations of the past few years is that TCDD cannot be considered by itself. Molecular biology has shown that the action of TCDD in a cell is receptor mediated and that there are a number of dioxinlike compounds that can all have toxic effects.

This receptor-mediated action for TCDD was first discovered in 1976 in Alan Poland's lab at the University of Wisconsin, Madison. Poland and others injected low levels of TCDD into animals and found that one of the first things that happened was the induction of a particular cytochrome P450 microsomal enzyme that oxygenates substrates, such as the carcinogen benzo[a]pyrene, that accumulate in fatty tissues. The response depended on the dose and had a great deal of potency. Researchers also noted that other planar chlorinated dioxins, dibenzo-

furans, and polychlorinated biphenyls (PCBs) could elicit a similar response, although not so strong as TCDD.

The evidence, found first in chicken embryos and tissue culture, then in rats and other animals, looked like classic receptor-mediated transduction, very similar to the way steroid hormones are made in cells. The receptor was recognized as a soluble intracellular protein and was designated the Ah—for aryl hydrocarbon—receptor. One experiment that clinched the presence of this receptor was that mice, inbred to be genetically without the receptor, do not respond with enzyme induction when treated with TCDD. Although it is impossible to say for sure, all evidence points to only one receptor for TCDD, one that begins all TCDD cellular activity.

So TCDD gets into the cell, where it binds strongly to the Ah receptor. It was discovered, however, that this wasn't enough to generate induction of P450. Subsequent research identified another protein, a translocating factor, necessary for the complex to pass from the cytoplasm into the nucleus. This protein has just recently been cloned by Oliver Hankinson and coworkers at the University of California, Los Angeles, department of pathology and the Laboratory of Biomedical & Environmental Sciences at UCLA.

Once inside the nucleus, it seems that several—possibly as many as four or five—of these complexes attach

to a specific sequence on the cell's DNA. This, according to James P. Whitlock Jr. at Stanford University School of Medicine's department of pharmacology, distorts the DNA chain, allowing attachment of other binding proteins. These events lead to the transcription of messenger RNA that forms the cytochrome P450 or other enzymes that might be induced by TCDD. These steps, too, are typical of a steroid induction in cells.

TCDD is now known to affect several genes. The gene for the original cytochrome, which is now called P4501A1, and a second cytochrome, P4501A2, are just two examples. Others include a gene for glucuronyl transferase, glutathion-S-transferase, and aldehyde dehydrogenase. Researchers have identified some other genes activated by the TCDD complex but have not fully characterized the mechanisms yet.

Although the enzymes these genes produce are not believed to have anything to do with TCDD toxicity, it is clear that the TCDD complex is the mechanism through which TCDD exhibits a toxic effect. Studies done with the Ah-receptor-defective mice showed that all the different toxicities of TCDD measurable in mice-chloracne (in hairless mice), porphyria, cleft palate formation, teratogenesis, even death—were limited to the mice that had the high-affinity receptor. Structure activity relationship studies also confirm this, according to Whitlock. The more potent the ligand for the receptor, the more potent the biological response. TCDD is the strongest binding of all the dioxins and dioxinlike compounds. The conclusion is that all the biological and toxic effects of TCDD and dioxin-related compounds are mediated through this one receptor.

Exactly what the receptor is, is still unknown. So far, its structure has remained elusive, although some researchers are getting close. Scientists have noted, too, that small differences in the receptor occur among species. They know these receptors have different molecular weights, but they don't know what that might mean with respect to affinity for TCDD. The Ah receptor is similar to the receptor that induces steroid hormones, such as estrogen. Thus, some scientists have put the Ah receptor in the same family as steroid hormone receptors, although others are convinced there are differences.

One scientist working on the receptor model is Ellen K. Silbergeld, adjunct professor of toxicology at the University of Maryland, College Park. "TCDD's interaction with this receptor is very powerful," Silbergeld says. "From my perspective, it must be doing something very important in normal cell physiology. I take it as an assumption that somewhere there is a natural compound that responds to the Ah receptor and transduces a set of events very important in normal cells." Silbergeld and other researchers point out that toxicology research has often found the unnatural ligand for receptors before it finds the natural compound. Some scientists believe that finding this endogenous ligand, which TCDD apparently mumics, for the Ah receptor will be a central issue for TCDD research. The receptor was found for opiates before the body's own endorphins were discovered, for example.

The very high specificity that TCDD and other dioxinlike compounds have for the Ah receptor is key to the development of what is called toxicity equivalents, E cause other dioxins, dibenzofurans, PCBs, even logenated naphthalenes bind to the receptor arioducytochrome P4501A1, it is assumed that they can cau the same range of toxic effects as TCDD. Because TCD has the strongest affinity, it is given a toxicity equivale cy factor of 1, and all others are being compared to EPA has adopted a list of factors for calculating toxicit of these mixtures of compounds. For instance, a pe tachlorodibenzo-p-dioxin with four of its chlorines the 2,3.7, and 8 positions is given a value of 0.5. C tachlorodibenzo-p-dioxins have a toxic equivalency zero.

The implications for measuring health effects of a these chemicals in humans and animals is significant. means that no longer can TCDD really be considere alone, but only as part of a potential problem. Accoring to Linda S. Birnbaum, director of the environme. tal toxicology division of the EPA Health Effects R search Laboratory in Research Triangle Park, N.C. "There are suggestions that coplanar PCBs may be, fact, responsible for much of the toxicity equivalency human serum. In other words, in industrialized cou: tries, the background level of TCDD in people may be 7 ppt, and if you add the toxic equivalencies of all th other dioxins and furans, it gets up to about 30 ppt. you now add the toxicity equivalents of all the PCE you might say that people are actually walking arour with 100 ppt of dioxin equivalents in their body.

While arguments will persist on what toxi these levels of contaminants have on people, i. already significant data on their effects on fish an wildlife. Philip M. Cook of the EPA Environmental Rsearch Laboratory in Duluth, Minn., reports that troi in Lake Ontario have an average of 35 ppt TCDD. Rich ard E. Peterson at the Environmental Toxicology Cente and School of Pharmacy at the University of Wisconsi: Madison, reports that concentration of 65 ppt TCDD eggs of lake trout can cause 50% mortality. Peterssays newly hatched lake trout exposed to TCDD in t egg stage are the most sensitive to the lethal effects TCDD compared to any mammal, bird, or fish speciever investigated. Cook says, though, that TCDD co centrations were higher in the past. "The tendency h been for the concentration [in fish] to come down," } says. There are no archived fish samples for compar son, but Cook guesses peak concentrations occurre sometime in the 1960s. This observation agrees wit the finding by Kang that TCDD levels in humans ma be dropping too.

One of the problems facing EPA is how to measur the buildup of TCDD in organisms as the contaminar moves up the food chain. The agency presently assumes a bioaccumulation factor of 5000 for TCDD levels in water. This may be too low, argues Peter deFur, scientist working for the activist organization Enviror mental Defense Fund, who says EPA is using old dat. EDF recommends that the factor be raised to passo,000. On the other hand, Cook says their boast mate for bioaccumulation of TCDD in Lake Ontaritrout is on the order of 160,000.

Though death is obviously the worst biological effection

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of TCDD and dioxinlike compounds, other problems are serious as well. Cook says the levels of TCDD in Lake Ontario are probably leading to a lack of natural reproduction in fish. At the U.S. Fish & Wildlife Service in East Lansing, Mich., Timothy Kubiak is investigating the reproductive effects of TCDD on mink, the species most sensitive to the compound after guinea pigs. He says by examining the toxicity of each of the individual congeners in mink, and, depending on several factors, TCDD may contribute to only about 5% of the total toxicity, most of which comes from PCBs. Mink are a good species to study, Kubiak adds, because their sensitivity makes them a good sentinel for changing concentrations of pollutants.

One toxic effect may be sexual aberrations in birds and animals from exposure to dioxinlike compounds. Theo Colborn of the World Wildlife Fund in Washington, D.C., is monitoring research on the effects of organochlorine compounds on wildlife, and she says that researchers are reporting instances of hermaphroditic offspring, such as male birds with oviducts, and abnormal female-female pairings of birds. Colborn contends that this is happening because TCDD and the dioxinlike compounds are messing up the estrogen receptors on developing embryos at critical times. "One dose of TCDD to rats on day 15 of pregnancy, that's about when sexual differentiation occurs, found a dose response in demasculinization and feminization of male offspring," she says.

All the information on animal toxicity and the data on molecular chemistry are going to be taken into account during a major effort, now under way, that EPA is making to revise its programs for regulating TCDD. After publication of the Fingerhut study, and the scientific agreements that came out of the Banbury conference, EPA's Reilly told the agency it was time for a reassessment.

William Farland, head of EPA's Office of Health & Environmental Assessment for the Office of Research & Development, says, "The review includes five major activities. First is the evaluation of the biologically based dose response model for TCDD, taking into account the idea that TCDD is known to bind



Silbergeld: physiology of Ah receptor

to a specific receptor in cells. Second is an evaluation of the science in various aspects of health effects, including carcinogenicity, reproductive effects, immunotoxicology, acute and chronic effects, and human epidemiological data. The final three items are a health research component. an ecological research component, and an exposure reassessment component." The entire project is supposed to be completed by May 1992.

Reconsideration of its cancer model represents a major break with tradition for EPA. The present linearized multistage model for carcinogenicity does not work for receptor-mediated molecules because it does not allow for a threshold below which cancer would not occur. According to Farland, the EPA guidelines, however, do permit the

agency to change its model. "The 1986 cancer guidelines suggest that one ought to choose a dose response model with a biological rationale. TCDD provides a good example of a chemical [for which] a lot of good studies have been done, and we ought to be able to bring this information into our dose response analysis. So we think this is consistent with the agency's advice all along and is one of the best opportunities we have to put that advice into practice."

EPA's Birnbaum is heading the agency's research on health effects. "Basically there are three areas we are trying to address here. First, we are trying to define the dose response curves, focusing on the most sensitive

toxicological endpoints. Next, we are looking at enzyme induction, specifically cytochromes P4501A1 and P4501A2. Finally, we are trying to find out where people are with respect to these responses."

TCDD has many molecular effects that can now be measured. Ligand binding to the Ah receptor, nuclear occupancy of the activated complex, cytochrome induction, and immunotoxicity are examples. But each of these seems to happen at a different level of TCDD exposure. Birnbaum says EPA is focusing on the low-dose region of the response curves for these markers, looking for the most sensitive endpoints. When it comes to measuring effects of TCDD, cancer may be a poor indicator. Birnbaum says it looks like im-



Birnbaum: sensitive indicators needed

News Focus

munotoxicity may be the most sensitive indicator of TCDD effects, and this is clearly a problem.

Cytochrome induction has been considered one of the easiest responses to detect. The P4501A1 enzyme can be induced in most cells and animals. Measured in terms of the action of aryl hydrocarbon hydroxylase, the cytochromes are important because they can actually metabolize some environmental chemicals into suspected carcinogens, Birnbaum says. "These cytochromes are present in high concentration in the liver in response to TCDD and related chemicals," she says. It is interesting that the liver was where Kociba at Dow recognized TCDD as a carcinogen.

A simple test for the presence of cytochrome P4501A2 is being worked on. According to Birnbaum, the hydroxylase acts at a specific site on the caffeine molecule. By labeling caffeine with carbon-13 at that site and administering it to people, the 1A2 cytochrome can be detected because ¹³C-labeled carbon dioxide will be exhaled. "We are doing this now in experimental animals," Birnbaum says.

EPA's lab will be assessing the endpoints for 11 different responses in the same animal. The idea is to see at what dose responses occur. Birnbaum says the data will be used to develop a risk model that might tell EPA just where humans fit into the overall scheme of toxicity of TCDD and dioxinlike compounds. If one assumes that people are walking around with about 100 ppt of TCDD toxicity equivalents, the assessment would be a guideline as to what response might come from that. "We may see that 100 ppt is orders of magnitude below the toxicological inflection point," Birnbaum says, "and therefore not of great concern. On the other hand, if the current exposure levels put us right near that inflection point, then any additional exposure would be undesirable." She adds that EPA particularly needs to look at the issue of sensitive populations, such as subsistence fishermen and nursing infants, that might receive doses 10 to 20 times higher than the overall population.

A great deal has been made about the issue of there being so great a species difference in response to TCDD, Birnbaum savs. However, for most toxicological endpoints, such as death, researchers can find a species outlaver. In this case it may be guinea pigs, which die at exposures of less than 1 µg per kg body weight. For the related hamster, the dose at which half die may reach as high as 5000 µg per kg body weight. "But most species cluster their sensitivity somewhere within a 10-fold range," she says. "If you take other endpoints for TCDD, say developmental toxicity, the dose that will kill the developing fetus is essentially within an order of magnitude in the guinea pig, hamster, rat, and mouse. If you look at enzyme induction, the dose that causes a response in these animals is essentially the same. So lethality has been sort of a red herring.'

Looking at the endpoint information on humans shows that they fall into the same range of sensitivities, Birnbaum says. "For enzyme induction and chloracne, humans respond similarly to experimental animals. In in-vitro experiments, the concentrations of TCDD that result in cleft palate formation in the rat and in the human are essentially the same. For cancer, the recent

study by Fingerhut is at least compatible with the pothesis that the blood levels in the group that he creased cancer were similar to the blood levels in the rats that developed cancer in the Kociba study."

Birnbaum thinks there is no reason to believe that people are different from animals in their response to TCDD. "I think the Seveso data tell us that, in terms of lethality, we are not guinea pigs. At the highest doses received by residents near Seveso, if they had been guinea pigs, there would have been some deaths. But we never reached the levels of TCDD that would have killed rats or mice or monkeys or dogs or rabbits or minks or anything else."

EPA's review will bring up to date the scientific reasoning for TCDD toxicity. By merging the human epidemiology data, the animal toxicity information, and the molecular biology, a better level of understanding and maybe a firmer basis for regulation of this contentious chemical will emerge.

Silbergeld and Birnbaum both think the regulatory number for TCDD may not change much. Even though the response level for cancer is high, the response level for immunotoxicity may be very low, and the current safe intake calculation of 0.006 picogram per kg body weight per day may be in the right range. CDC's Houk has commented that the intake number seems too low. Given the history of TCDD, it is likely that politics and emotion will have as much say in the end as does science.

Politics and emotion have a lot to do with the pulic's fear of dioxin. Those embroiled in the public controversy have diverse views on why TCDD remains so persistently in the forefront of people's concerns. Stanford's Whitlock believes it is because the compound has become synonymous with horrible scenes of birth defects and cancer. "It has become a sort of prototype for certain groups who are concerned about the environment," he says.

Several people place the focus on the Vietnam veterans. The Air Force's Wolfe, for one, thinks, "It was so closely related to the Vietnam experience and the ill treatment a lot of the returning folks got." But he also says, "It is sort of a flagship issue of all environmental problems."

Houk says attention is rapt because of those who insist that TCDD be labeled the most toxic substance known to man. Joseph Walker from the Chlorine Institute concurs on that point, adding that it also may be because "dioxin" looks and sounds like "toxin."

But uncertainty may be the biggest reason people's concerns haven't been eased by science. NIOSH's Fingerhut speculates that people have never felt reassured by the information coming out. "It is hard to get answers for a problem like this, and they are long in coming," she says. Banbury conference organizer Gallo agrees. "I think the scare comes from some people saying there is no problem and others saying this is the most heinous compound man has ever created." At Maryland, Silbergeld blames the uncertainty on the government. "Primarily it's the government's fault that they can't come to a decision on TCDD regulation and stick to it."

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The Regulation of Gene Expression by 2,3,7,8-Tetrachlorodibenzo-p-dioxin*

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I. Background

THE SOCIOPOLITICAL climate in the U.S. during the 1960s helped draw attention to the chemical that we have come to know as "dioxin." In the first place, cognizance of the potential risks associated with environmental contamination was on the increase; for example, in 1962 the publication of Silent Spring by Rachel Carson (17) generated particular concern about the increasing use of pesticides and herbicides. At the same time, there was growing restiveness about the conduct of the Vietnam war; one particular tactic, chemical defoliation of the countryside (Operation Ranch Hand), again focused attention on the possible adverse effects of the herbicides used to kill crops and vegetation in Southeast Asia. One particular herbicide (Agent Orange) used in Vietnam was a 1:1 mixture of (the *n*-butyl esters of) 2,4-dichlorophenoxyacetic acid (2.4-D)† and 2.4.5-trichlorophenoxyacetic acid (2,4,5-T); both compounds were also widely used as weed killers in the U.S. In 1970, an article in the New Yorker by Thomas Whiteside (172) publicized the suspicion that 2,4,5-T might cause birth defects.

Against this background, the report (24) that 2,4,5-T was teratogenic in rodents understandably aroused considerable concern among the public, environmental groups, the chemical industry, U. S. regulatory agencies, and Congress and led to restrictions on the use of the

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† Abbreviations used are: AHH, aryl hydrocarbon hydroxylase; δ-ALAS, δ-aminclevulinic acid synthetase; HAH, halogenated aromatic hydrocarbon; PAH, polycyclic aromatic hydrocarbon; TCDD, 2,3,7,8-tetrachlorodibenzo-p-dioxin; 2,4-D, 2,4-dichlorophenoxyacetic acid; 2.4,5-T, 2,4,5-trichlorophenoxyacetic acid; 3MC, 3-methylcholanthrene; βNF, β-naphthoflavone; CAT, chloramphenicol acetyltransferase; DRE, dioxin-responsive element; GRE, glucocorticoid-responsive element; HMG, high-mobility group; LD₅₀, median lethal dose; ED₅₀, median effective dose; BP, benzo(a)pyrene; QSAR, quantitative structure-activity relationship; DBBD, 2,2-dimethyl-5-t-butyl-1,3-benzo-dioxole.

herbicide. The results of subsequent studies (20, 23, 160) implied that the actual teratogen was probably 2.3.7.8tetrachlorodibenzo-p-dioxin (TCDD), a contaminant that forms during the commercial synthesis of 2,4,5-T (fig. 1). Public and scientific attention then shifted from 2,4,5-T to TCDD (often described simply as "dioxin") and its potential risk to human health. The remarkable potency of TCDD (in its acute lethality for guinea pigs), combined with the relative resistance of TCDD to chemical and biological degradation, contributed to the fear that soon was associated with the dioxin. Several industrial accidents, episodes of leakage or improper disposal of chemical waste, and lawsuits brought by veterans who might have been exposed to Agent Orange have tended to keep TCDD in the public eye ever since. Despite the scientific and lay scrutiny that dioxin has received, it has been difficult to document that TCDD poses a major health hazard for humans. Studies in animals reveal marked quantitative differences in their sensitivity to TCDD; for example, the acute oral median lethal dose (LD₅₀) of TCDD is about 5000-fold higher for the hamster than for the guinea pig. In addition, the qualitative spectrum of effects produced by chronic exposure to TCDD varies substantially among animal species (140). These observations make it unusually difficult to extrapolate the results of animal studies to man. Long-term follow-up of individuals exposed to TCDD in an industrial setting does not implicate the dioxin as a cause of excess mortality or serious morbidity for humans (110, 161, 180). However, the number of individuals followed has been relatively small.

Its teratogenic effects in rodents stimulated scientific interest in TCDD and related chlorinated hydrocarbons. By the early 1960s, TCDD had been implicated in the etiology of chloracne in humans (6, 90, 91) and chick edema disease (69), but its other effects and its mechanism of action were unknown. Today, we know that

FIG. 1. Formation of 2,3,7,8-tetrachlorodibenzo-p-dioxin (2,3,7,8-TCDD) during the synthesis of 2,4,5-trichlorophenoxyacetic acid (2,4,5-T). The first step in the industrial production of 2,4,5-T involves the alkaline hydrolysis of 1,2,4,5-tetrachlorobenzene (TCB) to form sodium 2,4,5-trichlorobenzeneoxide (TCBO). In the second step, TCBO reacts with chloroethanoate to form 2,4,5-T. If the temperature of the first step exceeds about 160°C, two molecules of TCBO can react in a double nucleophilic displacement to form 2,3,7,8-TCDD. Higher temperature and higher pH increase the formation of 2,3,7,8-TCDD. The side reaction is itself exothermic, possibly leading to even higher temperatures and uncontrolled reaction conditions (108, 143).

TCDD elicits a broad spectrum of biological effects, which vary according to the system in which the compound is tested. For example, in addition to its teratogenic effects, TCDD also produces several species- and tissue-dependent changes in epithelial tissues, immunological alterations, a wasting syndrome, tumor promotion, and the induction of several enzyme activities (139, 140). Therefore, models which seek to explain the mechanism of TCDD action must account for the diversity of effects that the compound produces. One reasonable hypothesis is that TCDD, acting by means of an intracellular receptor protein(s), alters the expression of a different set of genes in each TCDD-responsive cell type (54, 140). This particular model for TCDD action resembles that described for several steroid hormones, which also elicit diverse effects in receptor-dependent and tissue-specific fashion (146, 178). The evidence for and the molecular aspects of this model constitute the subject of

The development of TCDD-responsive cell culture systems, combined with the use of recombinant DNA and gene transfer methods, has facilitated the analysis of TCDD action at the molecular level. We now know that TCDD can activate the rate of transcription of a gene that encodes a specific cytochrome P-450 isozyme (see below). In addition, exposure to TCDD produces phenotypic changes suggestive of altered differentiation in epidermal cells in culture (53, 75, 93, 122, 145) and in cultured thymic epithelium (25, 52). Furthermore, TCDD promotes the expression of a transformed phenotype in C3H10T½ cells (1). Although the mechanism(s) by which TCDD produces these altered phenotypes is not yet known, it seems quite likely that changes in the expres-

sion of specific genes are involved. We also know that other halogenated aromatic hydrocarbons (HAHs) that are related structurally to TCDD (e.g., dibenzo-p-dioxins, dibenzofurans, biphenyls, biphenylenes, naphthalenes, and azoxybenzenes) produce similar patterns of toxicity, although the compounds differ greatly in potency. Therefore, we assume that these HAHs share a common mechanism of action. Because it is the most potent, TCDD is the prototype, and it has been studied much more intensively than the other HAHs.

Early studies (15, 55, 56) revealed that TCDD induces hepatic, drug-metabolizing enzyme activities that are catalyzed by cytochrome P-450 isozymes. This class of microsomal hemoproteins oxygenates lipophilic substrates and contributes to many different biological processes, ranging from steroid biosynthesis to chemical carcinogenesis (44, 99, 168). At the time when TCDD was beginning to undergo intensive study, certain chemicals were already known to induce one (or more) of the various cytochrome P-450 isozymes. The effect of TCDD was similar to that of 3-methylcholanthrene (3MC), a polycyclic aromatic hydrocarbon (PAH) that preferentially induces a specific form of cytochrome P-450 (designated cytochrome P-450c in the rat and cytochrome P_1 -450 in the mouse) (15, 55, 56). This particular cytochrome P-450 isozyme catalyzes aryl hydrocarbon hydroxylase (AHH) activity, which is present in many tissues and which is assayed using a simple and sensitive fluorescence technique (112). Therefore, measurement of AHH induction became a convenient way to determine if a particular tissue or cell type can respond to TCDD. (Note: the failure of TCDD to induce AHH activity in a particular cell type does not necessarily mean that the cell cannot exhibit some other response to the dioxin.) Given the long-established relationship between TCDD action and AHH induction, together with more recent achievements in the purification of cytochrome P-450 isozymes and the cloning of cytochrome P-450 genes (3, 173), it is not surprising that the most detailed knowledge of the mechanism of TCDD action has come from the study of TCDD-responsive cytochrome P-450 genes. We assume that TCDD influences the activity of other genes (i.e., those responsible for other phenotypic changes induced by the dioxin) by similar mechanisms. In retrospect, it is interesting that what began as a toxicological evaluation of a potent environmental contaminant has had unanticipated benefits. Analyses of TCDD action at the cellular and molecular levels have revealed a pathway by which an extracellular chemical signal can be transduced to the cell nucleus to activate the transcription of a specific gene. Further study of this TCDD-responsive signalling system in the future has the potential to reveal novel aspects of the mechanisms that control mammalian gene expression.

II. Evidence for a TCDD Receptor

The unusual potency of TCDD was the first clue that the dioxin might act through a specific receptor(s). For example, Poland and Glover observed that TCDD was orders of magnitude more powerful than other compounds in inducing both AHH activity and δ -aminolevulinic acid synthetase (δ-ALAS) activity in the chick embryo (131, 132). In addition, studies of TCDD congeners revealed a relationship between dioxin structure and potency as an inducer (132). On the basis of these data, Poland and Glover postulated that TCDD acts by means of an "induction receptor" to elevate AHH and δ -ALAS activities. They also suggested that the hypothetical receptor might mediate other effects of TCDD, because the potencies of the halogenated dibenzo-p-dioxins as enzyme inducers paralleled their toxic potencies. Subsequent studies of AHH induction in rat liver confirmed the potency of TCDD; the dioxin was 30,000-times more potent than the prototypical AHH inducer, 3MC (133).

The foregoing results naturally led to the study of TCDD-inducible AHH activity in inbred strains of mice that were known to respond differentially to 3MC. Two groups had shown that, in certain mouse strains (typified by C57EL/6), 3MC induced hepatic AHH activity; however, in other strains (typified by DBA/2), it did not. In crosses between these strains, AHH inducibility segregated as an autosomal dominant trait (133, 164). Furthermore, other responses to PAHs exhibited a similar segregation pattern (152). Therefore, the genetic locus that conferred these phenotypes was thought to be regulatory and was designated Ah (for aromatic hydrocarbon responsiveness). Mouse strains in which 3MC induced hepatic AHH activity were considered "responsive," a dominant trait governed by the Ah^b allele. Mouse strains in which 3MC did not induce hepatic AHH activity were considered "nonresponsive," a recessive trait governed by the Ah^d allele (50). Against this background, it was notable when Poland et al. reported that TCDD induced AHH activity to equally high levels in both C57BL/6 and DBA/2 mice (137). This observation indicated that the so-called nonresponsive DBA/2 strain could, in fact, exhibit a responsive phenotype if TCDD was the inducer instead of 3MC. This finding raised the possibility that the DBA/2 strain might contain an altered regulatory protein (i.e., receptor) to which 3MC bound poorly and, therefore, failed to elicit a response. However, the properties of TCDD might be such that it could still bind tightly enough to the altered receptor to induce AHH activity. The finding that the median effective dose (ED₅₀) for AHH induction by TCDD was about 20-fold higher in DBA/2 mice than in C57BL/6 mice was consistent with the idea that the DBA/2 strain contained a receptor with a lower binding affinity for the inducer (134). Subsequently, Poland et al., using [3H]TCDD and a charcoal/dextran binding assay, identified in C57BL/ 6 hepatic cytosol a protein which bound the dioxin saturably and with high affinity, thus providing biochemical evidence for the existence of a TCDD receptor. DBA/2 hepatic cytosol did not contain a detectable protein that bound TCDD with a similar high affinity. Furthermore, competition studies with TCDD congeners revealed that their binding affinities paralleled their induction potencies, suggesting a functional role for the receptor in the mechanism of AHH induction (136). These biochemical observations complemented the genetic evidence for the existence of a TCDD receptor. Because it is (presumably) encoded by the Ah locus, the TCDD receptor is also known as the Ah receptor.

The high affinity of TCDD for the TCDD receptor contributes to the high potency of the dioxin. In addition, TCDD's resistance to degradation means that the biological half-life of the compound is relatively long (9, 111, 123, 130). Thus, TCDD may produce sustained effects upon the cell, in comparison to those of other ligands for the receptor [e.g., 3MC or β -naphthoflavone (βNF) , whose biological half-lives are much shorter because the compounds are readily metabolized. It is not yet clear whether TCDD's ability to produce a prolonged biological response contributes substantially to the toxicity of the dioxin (54, 140). In addition, it is unclear why we have a receptor for TCDD at all. It is possible that the dioxin is only mimicking the binding of a "physiological" ligand to the receptor. However, the existence and properties of this hypothetical ligand (i.e., is it exogenous or endogenous; are its effects transitory or prolonged?) remain completely speculative (54, 140).

Studies of cells in culture have provided additional details about the involvement of a receptor in the response to TCDD. Hankinson exploited the observation of Gelboin et al. (45) that the PAH benzo(a)pyrene (BP) is toxic to cells that oxygenate the compound by means of the AHH system. Thus, he was able to select for AHHdefective cells by growth in the presence of BP (61). Miller and Whitlock took advantage of the fluorescence properties of BP and utilized the fluorescence-activated cell sorter to isolate cells that exhibit low (or no) AHH activity (107). Both groups identified two classes of receptor-defective mouse hepatoma cells. In one class, relatively few (i.e., 5 to 10% of wild-type) TCDD-receptor complexes form; however, those complexes that do form interact normally with a component(s) of the cell nucleus. These variants respond poorly to TCDD, as measured by AHH induction. In the other class, the formation of TCDD-receptor complexes appears normal. However, the complexes fail to interact normally at the nuclear level, and the variants fail to respond to TCDD at all. These results imply that AHH induction requires not only the formation of the TCDD-receptor complex but also a particular interaction between the complex and a component of the cell nucleus (97, 106). Cell fusion studies indicate that both variant phenotypes are recessive with respect to wild-type and that the variants belong to different complementation groups (62, 106). Thus, receptor function requires the contribution of (at least) two genes. The complementation analyses are open to several interpretations. One possibility is that the TCDD receptor has distinct subunits; perhaps, one gene encodes a TCDD-binding subunit, and a second gene encodes a chromatin-binding subunit. Another possibility is that the TCDD-receptor complex requires enzymatic modification to convert it to a chromatin-binding species; in this scenario, one gene encodes the receptor, and a second gene encodes the modifying enzyme. The available data do not allow us to distinguish between these and other possibilities. Progress in receptor purification and characterization should allow the testing of these hypotheses in the future.

Okey et al. (119) have analyzed the TCDD receptor in a clone of C3H/10T½ mouse fibroblasts in which some PAHs (and TCDD) induce AHH activity, but 3MC does not. [³H]3MC can bind to the receptor in cell extracts; however, it apparently is unable to do so in the intact cell. The basis for this interesting and unusual phenotype is unknown. More detailed studies of these cells (e.g., the dominant/recessive nature of the trait, structure-activity analyses of ligand binding) have the potential to reveal novel aspects of receptor structure and function in the future.

Genetic evidence for the Ah locus exists only in mice; phenotypes analogous to the responsive and nonresponsive mouse strains have not been observed in other species. However, other species, including humans, do contain a TCDD-binding protein(s) whose biochemical properties are similar to those of the mouse receptor (43, 68, 100). Therefore, the equivalent of the Ah locus presumably also exists in other species. In addition, crosses other than the prototypical C57BL/6 \times DBA/2 mating imply that the mouse Ah regulatory system may be quite complicated. In some crosses (e.g., $C3H/He \times DBA/2$), the induction of AHH activity by 3MC segregates as a codominant trait; this finding may indicate the existence of a third Ah allele (163). Furthermore, there is a single report that, in the C57BL/6N × AKR/N mating, the dominance is reversed, and the nonresponsive phenotype segregates as an autosomal dominant trait (148). This unusual observation, if confirmed, remains to be explained Therefore, additional studies of these inbred mouse strains and their progeny seem worthwhile, in order to determine if the genetic findings are associated with differences in TCDD receptor structure or function.

The chromosomal location, organization, and structure of the Ah locus are unknown. Studies of somatic cell hybrids suggest that mouse chromosome 17 contains a gene that regulates AHH inducibility; however, there is no direct evidence that it encodes the receptor protein (98). Furthermore, the number of alleles at the Ah locus and the number of proteins encoded by the locus are unknown. Success in cloning the gene(s) for the TCDD receptor presumably will allow these issues to be addressed in the future.

III. Biochemical Properties of the TCDD Receptor

Assays of the TCDD receptor require measuring the specific binding of a radiolabelled ligand to a protein that is a minor component of a crude cell extract. The major problem is distinguishing between specific and nonspecific binding. The limited aqueous solubility of TCDD tends to increase nonspecific binding and compounds the difficulty of the assay. The potential usefulness of more hydrophilic ligands, such as 3MC or β NF, is negated by their substantially lower affinity for the receptor. Several investigators have utilized different techniques to improve upon the original assay, which employed dextrancoated charcoal to remove unbound [3H]TCDD (136). Either adsorption of ligand-receptor complexes to hydroxylapatite (41, 127) or precipitation of ligand-receptor complexes with protamine sulfate (26) is a convenient, simple, and rapid method for assaying large numbers of samples. However, compared to more complicated techniques, these procedures tend to lack specificity, because they do not reveal any properties of the molecules to which TCDD is bound. In contrast, assays which involve centrifugation of TCDD-labelled material through sucrose gradients (116, 166) can verify that the TCDD-binding species has the appropriate sedimentation coefficient; however, such techniques are time-consuming, expensive, and relatively impractical for large numbers of samples. Other assays, such as isoelectric focusing in polyacrylamide gels (16) and gel permeation chromatography (42), have similar limitations. In practice, a combined approach seems reasonable. Impurities in the radiolabelled TCDD (28), contamination of the cell or tissue extract with serum proteins (129), and the presence of other PAH-binding proteins in the cell extract (18, 65, 165, 181) can introduce substantial artifacts into studies of the TCDD receptor. These factors need to be considered when interpreting the experimental data.

Several investigators (28, 43, 65, 101, 129) have compared the properties of the TCDD receptor from various animal species and/or tissues to find differences that might account for the diversity of TCDD's effects. In general, the results reveal that the hydrodynamic properties and the ligand-binding properties of the TCDD receptor are similar, but not identical, in various systems. In solution, the receptor behaves as a larger species (apparent $M_r \sim 250,000$) in 0.1 M KCl and as a smaller species (apparent $M_r \sim 120,000$) at 0.4 M KCl. This behavior may reflect the dissociation of an oligomeric species as the ionic strength is raised. If so, we do not yet know whether the receptor is homomeric or heteromeric. Both the faster and slower sedimenting species behave as asymmetric molecules, with axial ratios in the range of 11 to 12. Dissociation constants for TCDD fall in the range of 0.1 to 2 nm, and, in liver tissue, the number of TCDD binding sites is in the range of 30 to 60 fmol/mg protein. Hydrodynamic differences among various TCDD receptors appear to be relatively small. For example, Denison et al. (28) found about a 10% difference between Sprague-Dawley rats and C57BL/6N mice in the relative molecular mass of the hepatic TCDD receptor. In addition, the rat receptor readily changes to the smaller, more slowly sedimenting form in 0.4 M KCl whereas the mouse receptor is relatively resistant to this salt effect. Furthermore, the rat and mouse receptors differ somewhat in their ligand-binding preferences. We do not know whether these biochemical variations are associated with meaningful differences in receptor function. Therefore, based on our present knowledge, differences in the properties of the TCDD receptor among animal species and/or tissues do not easily account for the qualitative and quantitative differences in TCDD's effects in various experimental systems.

Several investigators (18, 73, 165, 181) have characterized in rats and mice another intracellular protein(s) that binds PAHs (e.g., 3MC) with higher affinity than TCDD. The hydrodynamic and ligand-binding properties of this protein distinguish it from the TCDD receptor (18, 74). In addition, the production of the protein does not segregate with the Ah locus in inbred mouse strains (118). The function of this protein remains unknown; it might be involved in the regulation of the rat cytochrome P-450c gene (74). However, this remains to be demonstrated rigorously. The recent purification of the mouse protein (19) should allow the preparation of antibodies, which will be helpful in studying its structure and regulation in greater detail. If this PAH-binding protein does, in fact, influence gene expression, it will be interesting to compare its mechanism of action with that of the TCDD receptor.

Both the hydrodynamic properties of the TCDD receptor and its apparent mechanism of signal transduction are analogous to those of several steroid receptors (146, 178). These similarities have led several investigators to compare the properties of steroid and TCDD receptors in detail (178). The ligand-binding properties of the receptors are quite different; steroids do not exhibit high affinity for the TCDD receptor, and vice-versa. On the other hand, the TCDD receptor and the glucocorticoid receptor are similar with respect to their chromatographic behavior on DNA-cellulose and heparin-Sepharose (175). Studies involving limited proteolysis reveal that, like steroid receptors, the TCDD receptor has a ligand-biriding domain that is distinct from a DNAbinding domain (64, 175). Molybdate stabilizes the higher molecular weight, ligand-binding form of steroid receptors; the compound has less effect on the TCDD receptor (29). The significance of this observation is not clear. Overall, the results of biochemical studies reveal some relatively crude structural similarities between the TCDD receptor and steroid receptors. In addition, both the TCDD receptor and steroid receptors transduce their

respective chemical signals by mechanisms that appear similar at our relatively superficial level of knowledge (see below). These structural and functional similarities suggest that both types of receptor might belong to a family of proteins which evolved from a common ancestor. On the other hand, variant cells that contain defective TCDD receptors fall into several complementation groups, whereas, in the glucocorticoid-responsive system. the analogous receptor variants are all in the same complementation group (179). These genetic findings might reflect important structural or functional differences between the TCDD receptor and steroid receptors and could mean that the biochemical similarities between them do not reflect their evolution from a common ancestor. Purification and characterization of the TCDD receptor in the future will permit a more meaningful comparison with steroid receptors and a more rigorous evaluation of their possible evolutionary relatedness.

Several groups have characterized the ligand-binding site of the TCDD receptor using structure-activity analyses. Initial studies, involving several series of HAHs, revealed that the ligands with the highest binding affinity were essentially planar and would fit into a rectangle approximately 3×10 A, with halogen atoms at each corner (138, 140). However, this particular view of the binding site cannot easily account for the efficacy of ligands like 3MC or β NF, which are substantially different in structure from the HAHs. More recently, studies of a series of indoles (including β NF) suggested that viewing the binding site as a rectangle of 6.8×13.7 A could more easily account for all of the data (47).

Quantitative structure-activity relationship (QSAR) methods (10) have also been used to study the interactions between various ligands and the TCDD receptor. In this approach, one studies a series of structurally related ligands, whose physicochemical properties (e.g., hydrophobicity, electronegativity, hydrogen-bonding capacity, van der Waals volume) can be estimated in quantitative terms. Multiple linear regression analysis is used to determine which physicochemical property(s) correlates with the ligand's ability to produce the effect being studied (e.g., binding to the receptor). Safe and coworkers (150) found that the binding affinity of 33 chlorinated dibenzo-p-dioxins and dibenzofurans correlated with the hydrophobicity of the compounds (within limits imposed by the volume of the ligand). These observations imply that the ligand-binding site of the TCDD receptor is very hydrophobic (31, 32, 150). QSAR analysis of a series of halogenated biphenyls suggested that, for these ligands, hydrophobicity, electronegativity, and hydrogen bondaccepting ability all enhance ligand-receptor binding (5). One potential limitation of the QSAR approach is that the data may not be amenable to unambiguous interpretation. For example, McKinney and coworkers have interpreted the halogenated biphenyl binding data to mean that dispersive interactions are the primary forces that 152 WHITLOCK

stabilize the ligand-receptor complex (102, 103). A second, and perhaps more serious, limitation of the QSAR approach involves the potential artifacts associated with the study of very insoluble ligands. For example, in some cases, the dissociation constant calculated for receptor binding substantially exceeds the aqueous solubility of the ligand. This raises questions as to the biological significance of the binding data. In general, the QSAR analyses suggest that the interactions which stabilize ligand-receptor binding are primarily hydrophobic, but can vary to some extent, depending upon the properties of the ligand. The ligand-binding site appears to be a hydrophobic pocket of somewhat undefined volume. It is conceivable that the binding site is somewhat flexible: the receptor might undergo small changes in conformation so as to optimize the binding interactions for any given ligand. To put the QSAR data in some perspective, it is worth noting that a thermodynamic analysis of glucocorticoid-receptor interactions implies that the forces which stabilize the hormone-receptor complex in that system are also primarily hydrophobic (177).

In the future, the QSAR approach might provide clues about the function of the TCDD-receptor complex. For example, Denomme et al. observed that, for two series of chlorinated dibenzo-p-dioxins and dibenzofurans, the receptor binding affinity correlated with lipophilicity alone, whereas the ability to induce AHH activity correlated with lipophilicity plus a steric factor (31, 32). These findings suggest that the formation of a ligandreceptor complex does not by itself suffice to evoke a biological response. Denomme et al. (31, 32) infer that the ligand-receptor complex must undergo a subsequent biochemical change(s) (perhaps conformational) in order to become functional. This interpretation is consistent with other studies of the TCDD receptor, involving different experimental techniques (see below). Also, in studies of the estrogen receptor, Hanson and Gorski, using a thermodynamic analysis, have reached a similar conclusion (66). Overall, despite its limitations, the QSAR approach appears useful for studying TCDD receptor structure and function in the future, particularly if used in conjunction with other experimental approaches.

Despite its biochemical similarities to steroid receptors, the TCDD receptor has been refractory to substantial purification by techniques used successfully for steroid receptors. Several factors have contributed to the difficulty. First, the relatively low receptor concentration (of the order of 10⁵ molecules/cell, assuming one TCDD-binding site per receptor) necessitates extensive purification. Second, like many proteins, the receptor tends to interact nonspecifically with other macromolecules during attempts at purification. Third, the extreme hydrophobicity of the ligand, combined with low receptor concentrations, aggravates the problem of nonspecific binding. Fourth, the noncovalent nature of ligand binding does not permit the use of denaturing procedures. To

address the last factor, Poland et al. (135) have synthesized an 125I-labeled, 2-azido-3-iodo-7,8-dibromodibenzop-dioxin as a photoaffinity reagent. They have used this compound to specifically covalently label in C57BL/6J mouse liver a protein that is likely to be the TCDD receptor (135). The protein migrates in denaturing polyacrylamide gels with an apparent molecular weight of about 95,000. The development of this reagent will permit a substantially greater degree of receptor purification (albeit in denatured form) than has previously been possible. In principle, this will lead to the generation of antibodies, which would be very powerful reagents for studying the structure and function of the TCDD receptor and could permit the cloning of its gene(s). Thus, studies during the next few years may produce substantial advances in our knowledge of the biochemical properties of the TCDD receptor.

IV. Function of the TCDD Receptor

Our understanding of the mechanism by which the TCDD receptor transduces a chemical signal into a cellular response is sketchy. Much of the current thinking is based on the apparent functional analogies between the TCDD receptor and steroid receptors, which have been studied more extensively. The hydrophobic ligand apparently enters the cell by passive diffusion; there is no evidence that active transport is required. The binding of TCDD to its receptor occurs inside the cell and apparently requires both ATP (58) and reduced sulfhydryl groups (30, 88). These findings may mean that the TCDD receptor undergoes cyclic phosphorylation/dephosphorylation during signal transduction and that the cell contains an enzyme system that can maintain the receptor in a reduced state. However, these hypotheses remain to be tested.

The location of the unoccupied receptor in the intact cell is open to question. In homogenates of untreated cells, the unoccupied receptor distributes primarily to the cytosolic fraction; conversely, in homogenates of TCDD-treated cells, the ligand-receptor complex distributes largely to the nuclear fraction (116, 117). One interpretation of these data is that, in the intact cell, the unoccupied receptor is in the cytoplasm and that ligand binding produces a "translocation" of the TCDD-receptor complex to the nucleus (116, 117). However, the TCDD receptor can redistribute between cytoplasm and nucleus during cell homogenization and fractionation (27, 174). Therefore, data from broken-cell experiments are difficult to interpret unambiguously. An alternative interpretation is that the unoccupied receptor is primarilv nuclear and that the binding of TCDD increases the affinity of the ligand-receptor complex for a nuclear component (e.g., chromatin), thus reducing the tendency of the complex to redistribute into the cytosol during cell fractionation (174). Studies of the distribution of the TCDD receptor in cells enucleated by cytochalasin B are also difficult to interpret unambiguously because exposure of cells to the antibiotic results in the loss of most TCDD-binding activity (59). Analogous studies of steroid receptors in cell homogenates are not particularly helpful either; for example, under aerobic conditions, the unoccupied estrogen receptor appears to reside in the nucleus (92, 171), whereas the unoccupied glucocorticoid receptor is apparently cytoplasmic (4). Interestingly, in ATP-depleted cells, the unoccupied glucocorticoid receptor appears to be nuclear (104). This may mean that the release of receptors from the nucleus is an energy-requiring event. Perhaps the simplest interpretation of the available data is that, in the intact cell, the unoccupied TCDD receptor is neither entirely cytoplasmic nor entirely nuclear but is in equilibrium between the two compartments.

Despite the uncertainty about the intracellular location of the unoccupied TCDD receptor, it seems clear that the biological response to TCDD requires an action of the inducer-receptor complex at the nuclear level. The most compelling evidence on this point stems from studies of receptor-defective cells. Two groups have isolated variant mouse hepatoma cells in which the TCDD-receptor complex apparently forms normally, but the complex binds weakly to a component of the nucleus (97, 106). This class of variant cells fails to transcribe the cytochrome P₁-450 gene in response to TCDD (63, 77, 78). These findings imply that, in order to evoke a response, the TCDD-receptor complex must interact with an element in the cell nucleus.

The phenotype of these variant cells implies that the binding of TCDD to its receptor is not sufficient to generate a functional inducer-receptor complex. This conclusion is consistent with the observation that, if the TCDD-receptor complex forms at 4°C (as opposed to 37°C), it fails to bind strongly to the nucleus (117, 174). Thus, the generation of a functional TCDD-receptor complex apparently requires a temperature-dependent "activation" event(s). The temperature-dependent step has the effect of increasing the affinity of the TCDDreceptor complex for nuclear binding sites, presumably on chromatin (116, 174). In addition, ligand binding enhances the affinity of the TCDD receptor for DNAcellulose or DNA-Sepharose in vitro (40, 64). However, we know virtually nothing about the mechanism of activation. For example, the temperature dependence could reflect a conformational change in the TCDD-receptor complex or a dissociation of subunits (which could expose a chromatin-binding domain), an enzymatic modification of the complex (which could alter its affinity for a nuclear binding site), or a combination of such events. In fact, studies of estrogen and glucocorticoid receptors suggest that several steps occur during the activation of the steroid-receptor complex to its functional form (67, 153, 154, 158). More detailed biochemical analysis of the activation phenomenon (e.g., after antibodies for the TCDD receptor become available) seems to be a potentially fruitful area for future research. In addition, the isolation of variants in the activation pathway would permit genetic analyses of the event(s) involved.

The interaction of the activated TCDD-receptor complex with the nucleus can lead rapidly to a biological response. For example, the increase in cytochrome P₁-450 gene transcription is half-maximal about 15 min after exposure of mouse hepatoma cells to TCDD (78). Furthermore, the response occurs in the absence of ongoing protein synthesis (76). These findings imply that the TCDD-receptor complex can activate gene transcription directly, without a requirement for intervening biochemical events, such as the generation of "second messengers" or the induction of other proteins. Studies in XB mouse teratoma cells support this conclusion, in that no evidence for the participation of several second messengers in the response to TCDD could be demonstrated (95).

We know very little about the factors that regulate the concentration of the TCDD receptor within the cell. There is disagreement in the literature as to whether exposure to TCDD-like ligands alters the intracellular receptor concentration (33, 157). However, the experiments are inherently difficult to interpret, because the only way to measure the receptor is with a ligand-binding assay, and the hydrophobicity of the ligand makes the studies technically difficult. In the future, it will be interesting to determine if TCDD regulates the expression of the TCDD receptor gene by a feedback mechanism, as may occur in the glucocorticoid-responsive signalling system (121). Such studies await the development of antibody probes for the TCDD receptor and the cloning of the TCDD receptor gene. A priori, there is no obvious reason to think that other inducers of cytochrome P-450 enzyme activities should influence the level of the TCDD receptor within the cell. (See ref. 173 for a discussion of the cytochrome P-450 isozymes and the different types of cytochrome P-450 inducers.) Yet. several investigators have reported that compounds of the "phenobarbital type" produce a 2- to 3-fold increase in the concentration of the hepatic TCDD receptor in rats and mice (33, 120). We know neither the mechanism by which this effect occurs nor its functional significance. Other workers have reported that 2,2-dimethyl-5-t-butyl-1,3-benzodioxole (DBBD), which is an "isosafrole type" of cytochrome P-450 inducer, apparently produces about a 2-fold decrease in the hepatic TCDD receptor in Dub:ICR and C57BL/6 mice (22). Again, the mechanism by which this reduction occurs is unknown. Furthermore, DBBD-treated mice also exhibit decreased enzyme induction in response to 3MC (a "TCDD-type" ligand), suggesting that the decrease in the TCDD receptor is functionally significant. However, this result seems to conflict with findings in C57BL/6 × DBA/2 mice, which indicate that a 2-fold reduction in receptor concentration has no apparent effect on maximal AHH induction by

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TCDD (101). Overall, it seems premature to draw firm conclusions about the regulation of the intracellular TCDD receptor concentration and the quantitative relationship between receptor concentration and a particular biological response. Development of antibody probes for the receptor will greatly facilitate the experimental analysis of these issues in the future.

V. TCDD-responsive Genomic Elements

Studies in variant cells imply that the induction of cytochronie P-450 gene transcription requires an interaction(s) between the TCDD-receptor complex and an element in the cell nucleus (78). Furthermore, the TCDD-receptor complex is a DNA-binding protein (40, 64). These observations suggested that the inducer-receptor complex might act at a "genomic switch" that is located near the start site of transcription for the cytochrome P₁-450 gene. To test this idea, several groups have utilized a strategy (87) that involves (a) ligating the putative genomic switch to a heterologous "indicator" gene and (b) testing the hybrid gene for function by transfection (fig. 2). For example, in studies of mouse hepatoma cells, Jones et al. (83) isolated DNA from the region upstream of the cytochrome P₁-450 gene, ligated it to the bacterial chloramphenicol acetyltransferase (CAT) gene, and transfected the recombinant molecules into cells that contained a normal TCDD receptor. TCDD induced CAT activity in the transfected cells, implying that the hybrid gene contained a TCDD-responsive DNA element. Furthermore, CAT induction had the expected sensitivity (ED50) to TCDD, and other ligands such as 3MC and β NF also induced CAT expression. Transfection of the hybrid gene into receptordefective variant cells resulted in loss of TCDD responsiveness, indicating that the induction of CAT activity

FIG. 2. Identification of dioxin-responsive elements. The top diagram depicts a TCDD-inducible gene (e.g., cytochrome P₁-450), containing a dioxin-responsive element (DRE) and a promoter (P), which are located upstream of the transcription start site (arrow). The middle diagram depicts the control region, which has been isolated from its homologous structural gene after cleaving the DNA with a restriction endonuclease(s). The bottom diagram depicts a hybrid gene, constructed by ligating the control region to a heterologous indicator gene, whose product (mRNA or protein) is convenient to assay. In the hybrid, the indicator gene (in principle) becomes responsive to TCDD. This hypothesis is tested by transfecting the hybrid gene into suitable (i.e., receptor-positive) cells, and determining if TCDD induces the product of the indicator gene. A positive result implies that the control region contains a DRE.

required a functional TCDD receptor. Together, these observations imply that the DNA that flanks the 5'-end of the cytochrome P₁-450 gene contains a domain(s) that functions as a dioxin-responsive element (DRE). Other workers have used a similar approach to find TCDDresponsive domains upstream of the cytochrome P₁-450 gene in C57BL/6 mice (49) and in the corresponding cytochrome P-450 genes in rats (39, 159) and humans (85). Thus, the current evidence suggests that TCDD acts by similar mechanisms in these different species. Furthermore, the functions of the TCDD receptor and its cognate DRE apparently have been conserved during evolution. For example, the DRE of the mouse responds to TCDD even when transfected into human cells (82), and the genomic elements of the rat (39, 159) and human (85) function when transfected into mouse cells. Thus, the TCDD receptor from one species apparently can recognize and act at a DRE from a heterologous species. These findings imply that the TCDD-responsive signalling system evolved prior to the divergence between mouse and man. Future studies in other species may substantiate this point more firmly. From an evolutionary standpoint, it is interesting that even some bacteria activate gene transcription by means of a receptor-dependent mechanism that responds to certain flavones as chemical signals (35, 125, 144). This (or a similar) system might represent the forerunner of the TCDD-responsive pathway present in eukaryotic cells.

The DNA that flanks the 5'-end of the cytochrome P₁-450 gene in mouse hepatoma cells contains other regulatory components in addition to the DRE. Jones et al. (83) used an exonuclease to produce progressively smaller DNA fragments, which were tested for function by transfection, after insertion into a CAT expression vector. These deletion analyses revealed an element that appears to function as a transcriptional promoter and confers constitutive expression upon the CAT gene. Still another functional domain is located at least 600 base pairs upstream of the promoter and acts to inhibit promoter function. Presumably, this inhibitory element interacts with a regulatory process (i.e., a repressor), although this hypothesis remains to be tested. Furthermore, the mechanism by which inhibition occurs from such a distance is unknown; the situation is reminiscent of "silencer" elements in other systems (12, 96). The TCDD-responsive genomic domain is located upstream of the inhibitory element, at least 1500 base pairs away from the transcription start site. The ability to activate transcription from a distance is typical of "enhancer" control systems. This observation provided a clue that the TCDD-responsive element might function as a transcriptional enhancer (see below). Together, the deletion analyses indicate that the DNA which flanks the 5'-end of the cytochrome P₁-450 gene in mouse hepatoma cells contains a combination of (at least) three different genomic control elements, each of which presumably interacts with specific regulatory proteins. Gonzalez and Nebert (49) have made similar observations in a C57BL/6 mouse liver system. Thus, in the case of the cytochrome P_1 -450 gene, the TCDD-responsive system functions in a context that also includes inhibitory and constitutive regulatory components. This sort of combinatorial control of transcription may prove to be typical of many eukaryotic genes (14).

Transcriptional enhancers are DNA elements that bind specific proteins and thereby augment gene expression. In contrast to other types of regulatory components (e.g., promoters), enhancers function relatively independently of their distance and orientation with respect to the regulated gene (89, 156). The ability of the TCDDresponsive domain to function at a distance from the transcription start site suggested that the DRE might be an enhancer (83). To test this possibility, Jones et al. isolated the TCDD-responsive domain and inserted it into a CAT expression vector, which was designed to evaluate the enhancer properties of the insert. Analyses of the recombinants by transfection revealed that (a) the DRE can function independently of the inhibitory and constitutive regulatory components to which it is linked in vivo; (b) the DRE can activate transcription from a heterologous promoter; (c) the DRE functions relatively independently of its distance from the promoter; and (d) the DRE functions relatively independently of its orientation with respect to the promoter. These findings indicate that the DRE has properties characteristic of enhancers. Transfections into receptor-defective variant cells revealed that the DRE requires a functional TCDD receptor (82). Therefore, the DRE, together with the TCDD receptor, constitutes a dioxin-responsive enhancer system. Others have made similar observations using an analogous experimental approach (39, 115). The mechanism(s) by which enhancers activate transcription from a distance is unknown. For example, enhancers might (a) produce a change in chromatin structure that can be propagated and that converts the nucleoprotein to a "transcriptionally active" form, (b) provide a binding site for a factor(s) that then "slides" along the genome to the promoter and initiates transcription, or (c) produce "looping" of the genome and the formation of a stable nucleoprotein complex that is required for the activation of transcription (37, 142). The TCDD-responsive enhancer constitutes a system appropriate for testing these hypotheses in the future.

The fact that the dioxin-responsive signalling pathway can function relatively independently of the other control components (i.e., constitutive and inhibitory) to which it is linked would appear to increase the versatility of the system as a mechanism for regulating gene expression. In principle, the system could function in diverse regulatory contexts that generate different patterns of gene expression. To begin to test this concept, Jones et al. (82) inserted into a CAT expression vector both a DRE

and a glucocorticoid-responsive element (GRE) in two different linear arrangements. When the DRE was positioned upstream of the GRE (i.e., the arrangement was 5'-DRE-GRE-promoter-CAT-3'), both TCDD and dexamethasone induced CAT activity independently, and CAT expression was additive in the presence of both inducers. Thus, in this context, both the dioxin-responsive system and the glucocorticoid-responsive system appear to function relatively independently of each other. In contrast, when the DRE was positioned downstream of the GRE (i.e., the arrangement was 5'-GRE-DREpromoter-CAT-3'), TCDD by itself could induce CAT expression, but dexamethasone produced a response only if TCDD also was present. Thus, in this context, the dioxin-responsive system appears to exert a "permissive" effect on the glucocorticoid-responsive system. These findings suggest that two different inducible enhancer systems can become interdependent when linked and can exhibit altered responsiveness, depending upon the regulatory context in which they are placed. It is relatively easy to envision that, in other contexts, the response of a particular gene to TCDD may be a function not only of the TCDD-responsive system itself but also of the other control components with which it is linked. This might be a mechanism which could account for (at least some of) the species and tissue specificity that is characteristic of the biological responses to TCDD. The interaction of the Ah and hr loci (94, 141) is a possible example of how regulatory systems might act in combination to control gene expression. In receptor-positive (Ah⁺) hairless (HRS/J) mice, TCDD produces epidermal hyperplasia and promotes skin papillomas only in homozygous animals (hr-/hr-) bearing a recessive mutation at the hr locus (94, 141). These observations may indicate the existence of a regulatory system that can block the response to TCDD. For example, suppose the hr locus encodes a regulatory protein that blocks gene expression by binding to a cis-acting genomic control element. Furthermore, suppose that the inhibitory (hr) system dominates the stimulatory (Ah) system when the two are linked. Then, a (hypothetical) keratinocyte gene that is under the control of both systems will not respond to TCDD unless the two hr alleles have been inactivated. This type of model might account for the responsiveness of hr^-/hr^- mouse skin to TCDD. The model makes predictions that are testable, in principle. However, the mechanisms by which control systems act in combination to regulate gene expression remain to be determined. Knowledge of the principles and mechanisms that govern combinatorial control of gene transcription appears fundamental to an understanding of major biological phenomena, such as differentiation or carcinogenesis. [See, for example, studies of the mouse alpha-fetoprotein gene (60)]. The TCDD-responsive system appears potentially useful for analyzing the mechanisms of combinatorial control in the future.

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The number of DREs in a regulatory hierarchy may also influence the response of the linked gene to TCDD. Deletion analyses suggested the presence of multiple TCDD-responsive elements upstream of the cytochrome P₁-450 gene (83). To examine this possibility, Jones et al. performed a more detailed study of the TCDD-responsive region in mouse hepatoma cells. Their findings revealed the existence of (at least) two distinct, nonoverlapping DNA fragments, each of which functions as a TCDD-responsive element when inserted into a CAT expression vector and transfected into wild-type cells. Transfections into receptor-defective cells imply that each element requires the TCDD receptor for its function. Each element has the properties of a transcriptional enhancer, and each can function independently of the other. The combined effects of the two elements are (at least) additive (81). Sogawa et al. (159) have also reported findings that are consistent with the existence of multiple TCDD-responsive domains upstream of the cytochrome P-450c gene of the rat. The significance of these observations is unknown at present. It is possible that the association of multiple DREs with the cytochrome P-450 gene is atypical and that other TCDD-responsive genes are linked to a single DRE. A second possibility is that multiple DREs are typical of TCDD-responsive genes and are advantageous in some way. For example, linking DREs in tandem may allow the formation of additional protein-protein interactions (e.g., between adjacent TCDD-receptor complexes) that stabilize a productive transcriptional complex, thereby permitting more effective gene expression. If so, then increasing the number of linked DREs might have a synergistic effect on gene expression. In addition, the spacing between DREs (which could affect protein-protein interactions) might also influence the response of the linked gene to TCDD (see, for example, refs. 11 and 162). Experiments designed to test these ideas are feasible in principle and may rever additional details of the mechanism of TCDD action in the future.

The advation of cytochrome P₁-450 gene expression requires both the TCDD receptor and the DRE. However, the act that both components are required does not necessarily demand that they physically interact during the process of signal transduction. To address this isom Durrin and Whitlock (36) utilized an assay which memures the accessibility of the DRE in situ (determined by its susceptibility to digestion by an exonucleasings a function of exposure of the cell to TCDD. Their in mouse hepatoma cells revealed that (a) a special NA region upstream of the cytochrome P1-450 protected from exonuclease digestion in TCDD is ced cells, but not in uninduced cells; (b) protective cells; (c) protecting occurs within 1 h of exposure of the cell to TCDD protection occurs in the absence of ongoing protein (Ehesis; (e) the protected region is in a domain that functions as a DRE. These observations imply that both the DRE and the TCDD-receptor complex contribute to the formation of a stable nucleoprotein structure that is relatively resistant to exonuclease attack. These findings strongly imply that the TCDD-receptor complex and the DRE interact in vivo to activate the transcription of the cytochrome P₁-450 gene. Others have made similar observations in studies of the glucocorticoid-responsive system (8). The details of the protein-DNA interactions and the possible participation of other proteins in the activation of gene transcription are interesting issues requiring additional research.

The properties of the chromatin recognition site(s) for the TCDD-receptor complex remain to be determined in more detail. Sogawa et al. (159) have proposed that the inducer-receptor complex recognizes a specific "consensus" decanucleotide sequence that is present in multiple copies in the DNA that flanks the 5'-end of the rat cytochrome P-450c gene. Interestingly, they observed that a synthetic concatemer of one such decanucleotide augmented the response of a linked CAT gene to 3MC. On the other hand, it is not yet clear that this effect is dependent upon the TCDD receptor, because the construct was not tested in receptor-defective cells. Also, two copies of the putative recognition sequence are located in a DNA region that does not exhibit responsiveness to 3MC (159). Thus, the specific chromatin structure that the TCDD-receptor complex recognizes remains uncertain. While a specific DNA sequence may be a necessary constituent of the recognition site, it may not be sufficient. In other systems, the binding of a regulatory protein to a specific DNA sequence does not generate a response unless additional specific proteinprotein interactions can also occur (13, 57, 71, 86). An analogous situation may also exist for the TCDD-responsive system. According to this view, the TCDD-receptor complex could bind to a specific DNA sequence; however, the binding will not produce a response unless the complex can also form additional interactions with other proteins that bind to adjacent regions of the genome. Thus, both DNA and protein would contribute to a functional recognition site for the TCDD-receptor complex.

VI. Future Prospects

The purification and characterization of TCDD receptors remain important areas of research for the future. Major advances in this area may occur during the next several years. For example, the ability to covalently label the receptor with an affinity reagent will allow the use of denaturing conditions during the isolation of the TCDD-binding protein; this will lead to a much greater degree of purification than has been possible previously. Antibodies raised against the purified protein (either in its denatured form or, possibly, after renaturation) should be useful reagents for studying the structural and functional domains of the receptor and for its isolation

using immunoaffinity techniques. Anti-receptor antibodies should permit more detailed analyses of receptor heterogeneity, receptor modification, receptor synthesis and degradation, and the temperature-dependent activation event that occurs during transduction of the TCDD signal. In addition, sequence analysis of the denatured protein should permit the synthesis of an oligonucleotide(s) that might be used to isolate the corresponding gene.

Other approaches to receptor purification may also be useful. For example, the functional similarities between TCDD receptors and steroid receptors suggest that structural similarities may also exist. Therefore, it may be possible to find antibodies, raised against purified steroid receptors, that cross-react with TCDD receptors. Such antibodies could be used in receptor purification. In addition, we may find that the TCDD-receptor complex recognizes a specific DNA sequence. If so, oligonucleotides that contain this sequence may be useful affinity reagents for the purification of the TCDD-receptor complex (see, for example, refs. 84 and 149).

Anti-receptor antibodies presumably could be used to clone the gene(s) for the TCDD receptor. An alternative approach might be to insert either genomic DNA or cDNA into an appropriate expression vector and to use the recombinant to complement the lesion in receptor-defective variant cells, with the selection procedure developed by van Gurp and Hankinson (167). Cloning and characterization of the TCDD receptor gene(s) will permit studies of its expression and lead to a better understanding of the factors which regulate the intracellular concentration of the receptor.

The TCDD receptor presumably consists of multiple functional domains, including a ligand-binding domain, a DNA (chromatin)-binding domain, and possibly, a domain(s) that interacts with other transcription factors. Cloning and expression of cDNA for the TCDD receptor, when combined with mutagenesis and gene transfer methodologies, should permit a detailed analysis of its functional domains (see, for example, refs. 46, 48, and 105). Furthermore, given the similarities between the TCDD receptor and steroid receptors described above, it will be intriguing to learn whether the TCDD receptor is a member of the hormone receptor family that is related to the viral erb A oncogene (51).

Variant cells have been very useful in characterizing the TCDD-responsive system to date; the study of additional variants would seem to be worthwhile in the future. For example, Hankinson and coworkers (62) have already identified by complementation analysis cells which presumably contain defects at other steps in the signal transduction pathway. In the future, the isolation of temperature-sensitive variants would allow us to analyze the reversibility of particular steps in signal transduction and to study the requirements for the maintenance of TCDD-induced changes in gene expression. Selection of

cells that overproduce TCDD receptors might be useful for purifying the receptor and for cloning its gene, as well as for studying quantitative aspects of signal transduction.

A great deal remains to be learned about the mechanism by which the dioxin-responsive element, together with the TCDD-receptor complex, functions as a transcriptional enhancer. Mutagenesis and gene transfer techniques can be used to define the functional boundaries of various DREs. DNA sequence analyses should reveal whether each DRE contains a specific sequence that forms part of the recognition site for the TCDDreceptor complex. The development of an enhancerdependent in vitro transcription system (see, for example, ref. 151) would facilitate the functional analysis of the dioxin-responsive pathway. In view of what is known about other enhancer systems (126, 155), it seems likely that the DRE will be found to interact with several other proteins, in addition to the TCDD-receptor complex. If so, the task of understanding the mechanism by which the inducer-receptor complex activates transcription will become substantially more complicated.

The chromatin structure (124, 169, 170) of TCDDresponsive genes is an interesting area for future study. For example, we know very little about the nucleoprotein organization of the DRE and other linked regulatory components (38). Are these elements associated with histones or other chromosomal [e.g., high-mobility group (HMG)] proteins? Are they organized into nucleosomes in vivo? If so, how do these structural features influence the function of the regulatory elements? If (as seems more likely) the DRE does not assume a nucleosomal structure in vivo, why not? What determines the chromatin structure of the DRE? Does the nucleoprotein structure of the element change upon its interaction with the TCDD-receptor complex? If so, is the structural alteration local or does it propagate along the chromatin fiber? What is the mechanism by which a change in structure leads to activation of gene transcription? Future studies that address these issues may generate interesting information that is relevant to transcriptional enhancement in general. In addition, studies in other systems suggest that transcriptionally active regions of chromatin may be preferentially associated with the nuclear matrix (80, 114). The role that the nuclear matrix plays in the cellular response to TCDD may also be a productive area for future research.

We know that TCDD induces the activity of UDP-glucuronyltransferase and NADPH:quinone reductase, apparently by activating the transcription of the corresponding gene (79, 147, 176). However, we do not yet know whether the activation of these other genes occurs in the absence of ongoing protein synthesis (i.e., if induction reflects a primary response to the TCDD-receptor complex). For example, others have proposed that TCDD induces a protein that secondarily activates a

battery of other genes (54, 140). In fact, some glucocorticoid-responsive genes appear to display this type of regulation (2, 7). The study of additional (i.e., noncytochronie P-450) TCDD-responsive genes might provide evidence for a protein(s) that mediates a TCDDinduced cascade of biological responses. The isolation and characterization of such a factor would be fundamental to our understanding of the mechanism by which TCDD elicits its diverse effects. The TCDD-responsive signalling system could also diminish the rate of transcription of some genes, either directly via the TCDDreceptor complex, or indirectly, via the synthesis of an inhibitory factor. This idea is testable, in principle. Also, the study of additional TCDD-responsive genes can increase our knowledge of how the dioxin-responsive enhancer system functions in other regulatory contexts, in combination with different promoters, silencers, and enhancers. Such information could make a valuable contribution to our understanding of the principles that govern the combinatorial control of gene transcription. Appropriate TCDD-responsive cell systems are available to begin the study of these problems (1, 25, 93, 122, 145).

The results of on-going epidemiological investigations suggest that exposure to TCDD poses less of a human health risk than was once feared, although the issue remains somewhat controversial (21, 70, 72, 109, 161). Most of us probably have accumulated some TCDD in our cells (123); however, it is not clear that this constitutes any measurable risk to the well-being of the general population. However, we cannot rule out the possibility that certain individuals are relatively susceptible to the effects of TCDD, either because of a genetic predisposition (34, 94, 141) and/or because of exposure to an additional environmental chemical(s). Future studies of TCDD action at the molecular level may ultimately help to clarify this issue and to resolve the uncertainty about the risk that dioxin poses to humans.

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REFERENCES

- 1. ABERNETHY, D. J., GREENLEE, W. F., HUBAND, J. C., AND BOREIKO, C. J.: 2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD) promotes the transformation of C3H/10T1/2 cells. Carcinogenesis (Lond.) 6: 651-653, 1985.
- 2. ADDISON, W. R., AND KURTZ, D. T.: Nucleotide sequences required for the regulation of a rat α_{2α}-globulin gene by glucocorticoids. Mol. Cell. Biol. 6: 2334-2346, 1986.
- 3. ADESNIK, M., AND ATCHISON, M.: Genes for cytochrome P-450 and their regulation. CRC Crit. Rev. Biochem. 19: 247-305, 1985.
 4. ANTAKLY, T., AND EISEN, H. J.: Immunocytochemical localization of glu-
- cocorticoid receptor in target cells. Endocrinology 115: 1984-1989, 1984.
- 5. BANDIERA, S., SAWYER, T., CAMPBELL, M. A., FUJITA, T., AND SAFE, S.: Competitive binding to the cytosolic 2,3,7,8-TCDD receptor: effects of structure on the affinities of substituted halogenated biphenyls—a QSAR approach. Biochem. Pharmacol. 32: 3803-3813, 1983.
- 6. BAUER, H., SCHULZ, K. H., AND SPEIGELBERG, U.: Occupational intoxications in manufacturing chlorophenol compounds. Arch. Gewerbepathol. Gewerbehyg. 18: 538-555, 1961.
- 7. BAUMANN, H., AND MAQUAT, L. E.: Localization of DNA sequences involved in dexamethasone-dependent expression of the rat α_1 -acid glycoprotein gene. Mol. Cell. Biol. 6: 2551-2561, 1986
- 8. BECKER, P. B., GLOSS, B., SCHMID, W., STRAHLE, U., AND SCHULTZ, G.: In vivo protein-DNA interactions in a glucocorticoid response element require the presence of the hormone. Nature (Lond.) 324: 686-688, 1986.

- 9. BIRNBAUM, L. S.: The role of structure in the disposition of halogenated aromatic xenobiotics. Environ. Health Perspect. 61: 11-20, 1985.
- 10. Blankley, C. J.: Introduction: a review of QSAR methodology. In Quantitative Structure-Activity Relationships of Drugs, pp. 1-21, Academic Press, New York, 1983.
- 11. Brady, J., Loeken, M. R., and Khoury, G.: Interaction between two transcriptional control sequences required for tumor-antigen-mediated simian virus 40 late gene expression. Proc. Natl. Acad. Sci. USA 82: 7299-7303, 1985,
- 12. Brand, A. H., Breeden, L., Abraham, J., Sternglanz, R., and Nas-MYTH, K.: Characterization of a "silencer" in yeast: a DNA sequence with properties opposite to those of a transcriptional enhancer. Cell 41: 41-48, 1985,
- 13. Brent, R., and Ptashne, M.: A eukaryotic transcriptional activator bearing the DNA specificity of a prokaryotic repressor. Cell 43: 729-736.
- 14. Brown, D. D.: The role of stable complexes that repress and activate eukaryotic genes. Cell 37: 359-365, 1984.
- 15. BUU-HOI, N. P., HIEN, D. P., SAINT-RUP, G., AND SERVOIN-SIDOINE, J.: Canceromimetic properties of tetrachloro-2,3,7,8-dibenzo-p-dioxin ("dioxin"). C. R. Acad. Sci. Paris **D272**: 1447-1450, 1971.
- 16. CARLSTEDT-DUKE, J., ELFSTROM, G., SNOCHOWSKI, M., HOGBERG, B., AND GUSTAFSFON, J. A.: Detection of the 2,3,7,8-tetrachlorodibenzo-pdioxin (TCDD) receptor in rat liver by isoelectric focusing in polyacrylamide gels. Toxicol. Lett. 2: 365-373, 1978.
- 17. Carson, R.: Silent Spring, 368 pp., Houghton Mifflin Co., Boston, MA, 1962.
- 18. COLLINS, S., AND MARLETTA, M.: Carcinogen-binding proteins. High-affinity binding sites for benzo(a)pyrene in mouse liver distinct from the Ah receptor. Mol. Pharmacol. 26: 353-359, 1984.
- 19. COLLINS, S., AND MARLETTA, M. A.: Purification of a benzo(a) yrene binding protein by affinity chromatography and photoaffinity labeling. Biochemistry 25: 4322-4329, 1986.
- 20. COLLINS, T. F. X., WILLIAMS, C. H., AND GRAY, G. C.: Teratogenic studies with 2,4,5-T and 2,4-D in the hamster. Bull. Environ. Contam. Toxicol. 6: 559-567, 1971.
- 21. COLTON, T.: Herbicide exposure and cancer. J. Am. Med. Assoc. 256: 1176-1178, 1986.
- 22. COOK, J. C., AND HODGSON, E.: Cytochrome P-450 induction by 3-methylcholanthrene and its antagonism by 2,2-dimethyl-5-t-butyl-1,3-benzodioxole. Biochem. Pharmacol. 35: 167-176, 1986.
- 23. COURTNEY, C. D., AND MOORE, J. A.: Teratology studies with 2,4,5-trichlorophenoxyacetic acid and 2,3,7,8-tetrachlorodibenzo-p-dioxin. Toxi-
- col. Appl. Pharmacol. 20: 396–403, 1971. 24. Courtney, K. D., Gaylor, D. W., Hogan, M. D., Falk, H. L., Bates, R. R., AND MITCHELL, I.: Teratogenic evaluation of 2,4,5-T. Science (Wash. DC) 168: 864-866, 1970.
- 25. DENCKER, L., HASSOUN, E., D'ARGY, R., AND ALM, G.: Fetal thymus organ culture as an in vitro model for the toxicity of 2,3,7,8-tetrachlorodibenzop-dioxin and its congeners. Mol. Pharmacol. 27: 133-140, 1985.
- 26. DENISON, M. S., FINE, J., AND WILKINSON, C. F.: Protamine sulfate precipitation: a new assay for the Ah receptor. Anal. Biochem. 142: 28-36, 1984,
- 27. Denison, M. S., Harper, P. A., and Okey, A. B.: Ah receptor for 2,3,7,8tetrachlorodibenzo-p-dioxin. Codistribution of unoccupied receptor with cytosolic marker enzymes during fractionation of mouse liver, rat liver, and cultured Hepa-1c1 cells. Eur. J. Biochem. 155: 223-229, 1986.
- 28. DENISON, M. S., VELLA, L. M., AND OKEY, A. B.: Structure and function of the Ah receptor for 2,3,7,8-tetrachlorodibenzo-p-dioxin. Species differences in molecular properties of the receptors from mouse and rat hepatic cytosols. J. Biol. Chem. 261: 3987-3995, 1986.
- 29. DENISON, M. S., VELLA, L. M., AND OKEY, A. B.: Hepatic Ah receptor for 2,3,7,8-tetrachlorodibenzo-p-dioxin: partial stabilization by molybdate. J. Biol. Chem. 261: 10189-10195, 1986.
- 30. DENISON, M. S., VELLA, L. M., AND OKEY, A. B.: Structure and function of the Ah receptor: sulfhydryl groups required for binding of 2,3,7,8tetrachlorodibenzo-p-dioxin to cytosolic receptor from rodent livers. Arch. Biochem. Biophys. 252: 388-395, 1987.
- 31. Denomme, M. A., Homonko, K., Fujita, T., Sawyer, T., and Safe, S.: Effects of substituents on the cytosolic receptor-binding avidities and aryl hydrocarbon hydroxylase induction potencies of 7-substituted 2,3-dichlorodibenzo-p-dioxins. A QSAR analysis. Mol. Pharmacol. 27: 656-661,
- 32. DENOMME, M. A., HOMONKO, K., FUJITA, T., SAWYER, T., AND SAFE, S.: Substituted polychlorinated dibenzofuran receptor binding affinities and aryl hydrocarbon hydroxylase induction potencies—a QSAR analysis. Chem.-Biol. Interact. 57: 175-187, 1986.
- 33. DENOMME, M. A., LEECE, B., LI, A., TOWNER, R., AND SAFE, S.: Elevation of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) binding by polychlorinated biphenyls. Biochem. Pharmacol. 35; 277-282, 1986.
- 34. Doss, M., Sauer, H., von Tiepermann, R., and Colombi, A. M.: Development of chronic hepatic porphyria (porphyria cutanea tarda) with inherited uroporphyrinogen decarboxylase deficiency under exposure to dioxin. Int. J. Biochem. 16: 369-373, 1984.

- 35. DOWNIE, J. A., AND JOHNSTON, A. W. B.: Nodulation of legumes by Rhizobium: the recognized root? Cell 47: 153-154, 1986.
- 36. DURRIN, L. K., AND WHITLOCK, J. P., JR.: In situ protein-DNA interactions at a dioxin-responsive enhancer associated with the cytochrome P1-450 gene. Mol. Cell. Biol. in press, 1980.
- 37. ECHOLS, H.: Multiple DNA-protein interactions governing high-precision DNA transactions. Science (Wash. DC) 233: 1050-1056, 1986.
- 38. Enick, L., Fagan, J., and Bustin, M.: Chromatin structure of the cytochrome F450c gene changes following induction. Biochemistry 25: 7062-7068, 1986,
- 39. Fujisawa-Behara, A., Sogawa, K., Nishi, C., and Fujii-Kuriyama, Y.: Regulatory DNA elements localized remotely upstream from the drugmetabolizing cytochrome P-450c gene. Nucl. Acids Res. 14: 1465-1477,
- 40. GASIEWICZ T. A., AND BAUMAN, P. A.: Heterogeneity of the rat hepatic Ah receptor and evidence for transformation in vitro and in vivo. J. Biol. Chem. 262: 2116-2120, 1987.
- 41. GASIEWICZ, T. A., AND NEAL, R. A.: The examination and quantitation of tissue cytosolic receptors for 2,3,7,8-tetrachlorodibenzo-p-dioxin using hydroxylapatite. Anal. Biochem. 124: 1-11, 1982.
- GASIEWICZ, T. A., AND RUCCI, G.: Examination and rapid analysis of hepatic cytosolic receptors for 2,3,7,8-tetrachlorodibenzo-p-dioxin using gel-permeation high performance liquid chromatography. Biochim. Biophys. Acta **798:** 37–45, 1984.
- 43. GASIEWICZ, T. A., AND RUCCI, G.: Cytosolic receptor for 2,3,7,8-tetrachlorodiber zo-p-dioxin. Evidence for a homologous nature among various mammalian species. Mol. Pharmacol. 26: 90-98, 1984.
- GELBOIN, Fl. V.: Benzo(a)pyrene metabolism, activation, and carcinogenesis: role and regulation of mixed-function oxidases and related enzymes. Physiol. Rev. 60: 1107-1166, 1980.
- 45. GELBOIN, H. V., HUBERMAN, E., AND SACHS, L.: Enzymatic hydroxylation of benzopyrene and its relationship to cytotoxicity. Proc. Natl. Acad. Sci. USA 64: 1188-1194, 1976.
- 46. GIGUERE, V., HOLLENBERG, S. M., ROSENFELD, M. G., AND EVANS, R. M.: Functional domains of the human glucocorticoid receptor. Cell 46: 645-652, 1936.
- 47. GILLNER, M., BERGMAN, J., CAMBILLAN, C., FERNSTROM, B., AND GUS-TAFSSON, J. A.: Interactions of indoles with specific binding sites for 2,3,7,8-tetrachlorodibenzo-p-dioxin in rat liver. Mol. Pharmacol. 28: 357-363, 1935.
- 48. GODOWSKI, P. J., RUSCONI, S., MIESPELD, R., AND YAMAMOTO, K. R.: Glucocorticoid receptor mutants that are constitutive activators of transcriptional enhancement. Nature (Lond.) 325: 365-368, 1987.
- 49. GONZALEZ, F. J., AND NEBERT, D. W.: Autoregulation plus upstream positive and negative control regions associated with transcriptional activation of the mouse P₁-450 gene. Nucl. Acids Res. 13: 7269-7288, 1985.
- 50. GREEN, M. C.: Guidelines for nomenclature of genetically determined biochemical variants in the house mouse, Mus musculus. Biochem. Genet. 9: 369-374, 1973,
- 51. GREEN, S., AND CHAMBON, P.: A superfamily of potentially oncogenic hormone receptors. Nature (Lond.) 324: 615-617, 1986.
- 52. GREENLEE, W. F., DOLD, K. M., IRONS, R. D., AND OSBORNE, R.: Evidence for direct action of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) on thymic epithelium. Toxicol. Appl. Pharmacol. **79**: 112–120, 1985.
- GREENLEE, W. F., DOLD, K. M., AND OSBORNE, R.: Actions of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) on human epidermal keratinocytes in culture. In Vitro Cell. Dev. Biol. 21: 509-512, 1985.
 54. GREENLEE, W. F., AND NEAL, R. A.: The Ah receptor: a biochemical and
- biological perspective. In The Receptors, ed. by M. Conn, Vol. 2, pp. 89-129, Academic Press, New York, 1985.
- 55. GRIEG, J. B.: Effect of 2,3,7,8-tetrachlorodibenzo-1,4-dioxin on drug metab-
- olism in the rat. Biochem. Pharmacol. 21: 3196-3198, 1972. 56. GRIEG, J. B., AND DEMATTEIS, F.: Effects of 2,3,7,8-tetrachlorodibenzo-pdioxin on drug metabolism and hepatic microsomes of rats and mice. Environ. Health Perspect. (no. 5): 211-219, 1973.
- 57. GRIFFITH, J., HOCHSCHILD, A., AND PTASHNE, M.: DNA loops induced by cooperative binding of λ repressor. Nature (Lond.) 322: 750-752, 1986.
- 58. GUDAS, J. M., AND HANKINSON, O.: Reversible inactivation of the Ah receptor associated with changes in intracellular ATP levels. J. Cell. Physiol. 128: 449-456, 1986.
- GUDAS, J. IM., KARENLAMPI, S. O., AND HANKINSON, O.: Intracellular location of the Ah receptor. J. Cell. Physiol. 128: 441–448, 1986.
- 60. HAMMER, R. E., KRUMLAUF, R., CAMPER, S. A., BRINSTER, R. L., AND TILGHMAN, S. M.: Diversity of alpha-fetoprotein gene expression in mice is generated by a combination of separate enhancer elements. Science (Wash. DC) 235: 53-58, 1987.
- 61. HANKINSON, O.: Single-step selection of clones of a mouse hepatoma line deficient in aryl hydrocarbon hydroxylase. Proc. Natl. Acad. Sci. USA 76: 373-376, 1979.
- 62. HANKINSON, O.: Dominant and recessive aryl hydrocarbon hydroxylasedeficient mutants of the mouse hepatoma line, Hepa-1, and assignment of the recessive mutants to three complementation groups Somatic Cell Genet. 9: 497-514, 1983.
- 63. HANKINSON, O., ANDERSON, R. D., BIRREN, B. W., SANDER, F., NEGISHI, M., AND NEBERT, D. W.: Mutations affecting the regulation of transcrip-

- tion of the cytochrome P_1 -450 gene in the mouse Hepa-1 cell line. J. Biol. Chem. 260: 1790-1795, 1985.
- HANNAH, R. R., LUND, J., POELLINGER, L., GILLNER, M., AND GUSTAFS-SON, J. A.: Characterization of the DNA-binding properties of the receptor for 2,3,7,8-tetrachlorodibenzo-p-dioxin. Eur. J. Biochem. 156: 237-242,
- 65. HANNAH, R. R., NEBERT, D. W., AND EISEN, H. J.: Regulatory gene product of the Ah complex: comparison of 2,3,7,8-tetrachlorodibenzo-p-dioxin and 3-methylcholanthrene binding to several moieties in mouse liver cytosol. J. Biol. Chem. **256**: 4584-4590, 1981.
- 66. HANSEN, J. C., AND GORSKI, J.: Conformational and electrostatic properties of unoccupied and liganded estrogen receptors determined by aqueous two-phase partitioning. Biochemistry 24: 6078-6085, 1985.
- 67. HANSEN, J. C., AND GORSKI, J.: Conformational transitions of the estrogen receptor monomer. Effects of estrogens, antiestrogens, and temperature. J. Biol. Chem. 261: 13990-13996, 1986.
- 68. HARPER, P. A., GOLAS, C. L., AND OKEY, A. B.: Characterization of the Ah receptor and arvi hydrocarbon hydroxylase induction by 2.3.7.8-tetrachlorodibenzo-p-dioxin and benz(a)anthracene in the human A431 squamous cell carcinoma line. Submitted for publication.
- HIGGINBOTHAM, G. R., HUANG, A., FIRESTONE, D., VERRETT, J., RESS, J., AND CAMPBELL, A. D.: Chemical and toxiocological evaluations of isolated and synthetic chloro derivatives of dibenzo-p-dioxin. Nature (Lond.) 220: 702-703, 1968.
- 70. HOAR, S. K., BLAIR, A., HOLMES, F. F., BOYSEN, C. D., ROBEL, F. J. HOOVER, R., AND FRAUMENI, J. F., JR.: Agricultural herbicide use and risk of lymphoma and soft-tissue sarcoma. J. Am. Med. Assoc. 256: 1141-1147, 1986.
- 71. HOCHSCHILD, A., AND PTASHNE, M.: Cooperative binding of λ -repressors to sites separated by integral turns of the DNA helix. Cell 44: 681-687,
- 72. HOFFMAN, R. E., STEHR-GREEN, P. A., WEBB, K. B., EVANS, R. G., KNUTSEN, A. P., SCHRAMM, W. F., STAAKE, J. L., GIBSON, B. B., AND STEINBERG, K. K.: Health effects of long-term exposure to 2,3,7,8-tetrachlorodibenzo-p-dioxin. J. Am. Med. Assoc. 255; 2031-2038, 1986.
- 73. HOLDER, G. M., TIERNEY, B., AND BRESNICK, E.: Nuclear uptake and subsequent nuclear metabolism of benzo(a)pyrene complexed to cytosolic proteins, Cancer Res. 41: 4408-4414, 1981.
- HOUSER, W. H., HINES, R. N., AND BRESNICK, E.: Implication of the "4S" polycyclic aromatic hydrocarbon binding protein in the transregulation of rat cytochrome P-450c expression. Biochemistry 24: 7839-7845, 1985.
- 75. HUDSON, L. G., TOSCANO, W. A., JR., AND GREENLEE, W. F.: 2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD) modulates epidermal growth factor (EGF) binding to basel cells from a human keratinocyte cell line. Toxicol. Appl. Pharmacol. 82: 481-492, 1986.
- 76. ISRAEL, D. I., ESTOLANO, M. G., GALEAZZI, D. R., AND WHITLOCK, J. P., JR.: Superinduction of cytochrome P1-450 gene transcription by inhibition of protein synthesis in wild type and variant mouse hepatoma cells. J. Biol. Chem. 260: 5648-5653, 1985.
- 77. ISRAEL, D. I., AND WHITLOCK, J. P., JR.: Induction of mRNA specific for cytochrome P₁-450 in wild type and variant mouse hepatoma cells. J. Biol. Chem. 258: 10390-10394, 1983.
- 78. ISRAEL, D. I., AND WHITLOCK, J. P., JR.: Regulation of cytochrome P₁-450 gene transcription by 2,3,7,8-tetrachlorodibenzo-p-dioxin in wild type and
- variant mouse hepatoma cells. J. Biol. Chem. 259: 5400-5402, 1984.
 79. IYANAI, T., HANIU, M., SOGAWA, K., FUJII-KURIYAMA, Y., WATANABE, S., SHIVELY, J. E., AND ANAN, K. F.: Cloning and characterization of cDNA encoding 3-methylcholanthrene inducible rat mRNA for UDP-glucuronosyltransferase. J. Biol. Chem. 261: 15607-15614, 1986.
- 80. JACKSON, D. A., AND COOK, P. R.: Transcription occurs at a nucleoskeleton.
- EMBO (Eur. Mol. Biol. Organ.) J. 4: 919-925, 1985.

 81. Jones, P. B. C., Durrin, L. K., Fisher, J. M., and Whitlock, J. P., Jr.:
 Control of gene expression by 2,3,7,8-tetrachlorodibenzo-p-dioxin: multiple dioxin-responsive domains 5'-ward of the cytochrome P₁-450 gene. J. Biol. Chem. 261: 6647-6650, 1986.
- JONES, P. B. C., DURRIN, L. K., GALEAZZI, D. R., AND WHITLOCK, J. P., JR.: Control of cytochrome P₁-450 gene expression: analysis of a dioxinresponsive enhancer system. Proc. Natl. Acad. Sci. USA 83: 2802-2806,
- 83. Jones, P. B. C., Galeazzi, D. R., Fisher, J. M., and Whitlock, J. P., JR.: Control of cytochrome P₁-450 gene expression by dioxin. Science (Wash. DC) 227: 1499-1502, 1985.
- 84. KADONAGA, J. T., AND TJIAN, R.: Affinity purification of sequence-specific DNA binding proteins. Proc. Natl. Acad. Sci. USA 83: 5889-5893, 1986.
- 85. KAWAJIRI, K., WATANABE, J., GOTOH, O., TAGASHIRA, Y., SOGAWA, Z., AND FUJII-KURIYAMA, Y.: Structure and drug inducibility of the human cytochrome P-450c gene. Eur. J. Biochem. 159: 219-225, 1986.
- 86. KEEGAN, L., GILL, G., AND PTASHNE, M.: Separation of DNA binding from the transcription-activating function of a eukaryotic regulatory protein.
- Science (Wash. DC) 231: 699-704, 1986. 87. KELLY, J. H., AND DARLINGTON, G. J.: Hybrid genes: molecular approaches to tissue-specific gene regulation. Annu. Rev. Genet. 19: 273-296, 1985.
- 88. KESTER, J. E., AND GASIEWICZ, T. A.: Characterization of the in vitro stability of the rat hepatic receptor for 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD). Arch. Biochem. Biophys. 252: 606-625, 1987.

- 89. KHOURY, G., AND GRUSS, P.: Enhancer elements. Cell 33: 313-314, 1983. 90. KIMMIG, J., AND SCHULZ, K. H.: Chlorinated aromatic cyclic ethers as a
- cause of the so-called chloracne. Naturwissenschaften 44: 337-338, 1957. 91. KIMMIG, J., AND SCHULZ, K. H.: Occupational acne (so-called chloracne) due to chlorinated aromatic cyclic ethers. Dermatologia 115: 540-546.
- 1957.
- 92. KING, W. S., AND GREENE, G. L.: Monoclonal antibodies localize oestrogen receptor in the nuclei of target cells. Nature (Lond.) 307: 745-747, 1984.
- 93. KNUTSON, J. C., AND POLAND, A.: Keratinization of mouse teratoma cell line XB produced by 2,3,7,8-tetrachlorodibenzo-p-dioxin: an in vitro model of toxic ty. Cell 22: 27-36, 1980.
- 94. KNUTSON, J. C., AND POLAND, A.: Response of murine epidermis to 2,3,7,8tetrachlorodibenzo-p-dioxin: interaction of the Ah and hr loci. Cell 30: 225-234, 1982,
- 95. KNUTSON, J. C., AND POLAND, A.: 2,3,7,8-Tetrachlorodibenzo-p-dioxin: examination of biochemical effects involved in the proliferation and differentiation of XB cells. J. Cell. Physiol. 121: 143-151, 1984.
- 96. LAIMINS, L., HOLMGREN-KONIG, M., AND KHOURY, G.: Transcriptional "silencer" element in rat repetitive sequences associated with the rat insulin 1 gene locus. Proc. Natl. Acad. Sci. USA 83: 3151-3155, 1986.
- 97. LEGRAVEHEND, C., HANNAH, R. R., EISEN, H. J., OWENS, I. S., NEBERT, D. W., AND HANKINSON, O.: Regulatory gene product of the Ah locus. Characterization of receptor mutants among mouse hepatoma clones. J. Biol. Chem. 257: 6402-6407, 1982.
- 98. LEGRAVEHEND, C., KARENLAMPI, S. O., BIGELOW, S. W., LALLEY, P. A., KOZAK, C. A., WOMACK, J. E., AND NEBERT, D. W.: Aryl hydrocarbon hydroxylase induction by benzo(a)anthracene: regulatory gene localized to the distal portion of mouse chromosome 17. Genetics 107: 447-461, 1984.
- Lu, A. Y. H., and West, S. B.: Multiplicity of mammalian microsomal cytochromes P-450. Pharmacol. Rev. 31: 277-295, 1979.
- 100. MANCHESTER, D. K., GORDON, S. K., GOLAS, C. L., ROBERTS, E. A., AND OKEY, A. B.: Ah receptor in human placenta: stabilization by molybdate and characterization of binding of 2,3,7,8-tetrachlorodibenzo-p-dioxin, 3methylcholanthrene, and benzo(a)pyrene. Cancer Res. in press, 1987.
- 101. MASON, M. E., AND OKEY, A. B.: Cytosolic and nuclear binding of 2,3,7,8tetrachlorodibenzo-p-dioxin to the Ah receptor in extra-hepatic tissues of rats and mice. Eur. J. Biochem. 123: 209-215, 1982.
- 102. McKinney, J. D., Darden, T., Lyerly, M. A., and Pedersen, L. G.: PCB and related compound binding to the Ah receptor(s). Theoretical model based on molecular parameters and molecular mechanics. Quant. Struct.-Act. Relat. 4: 166-172, 1985.
- 103. McKinney, J. D., Long, G. A., and Pederson, L.: PCB and dioxin binding to cytosol receptors: a theoretical model based on molecular parameters. Quant. Struct.-Act. Relat. 3: 99-105, 1984.
- 104. MENDEL, D. B., BODWELL, J. E., AND MUNCK, A.: Glucocorticoid receptors lacking hormone-binding activity are bound in nuclei of ATP-depleted cells. Nature (Lond.) 324: 478–480, 1986.
- 105. MIESFELI, R., RUSCONI, S., GODOWSKI, P. J., MALER, B. A., OKRET, S., WIKSTROM, A. C., GUSTAFSSON, J. A., AND YAMAMOTO, K. R.: Genetic complementation of a glucocorticoid receptor deficiency by expression of cloned receptor cDNA. Cell 46: 389-399, 1986.
- 106. MILLER, A. G., ISRAEL, D. I., AND WHITLOCK, J. P., JR.: Biochemical and genetic analysis of variant mouse hepatoma cells defective in the induction of benzo(a)pyrene-metabolizing enzyme activity. J. Biol. Chem. 258: 3523-3527, 1983.
- 107. MILLER, A. G., AND WHITLOCK, J. P., JR.: Novel variants in benzo(a)pyrene metabolism. Isolation by fluorescence-activated cell sorting. J. Biol. Chem. 256: 2433-2437, 1981
- 108. MILNES, M. H.: Formation of 2,3,7,8-tetrachlorodibenzodioxin by thermal decomposition of sodium 2,4,5-trichlorophenate. Nature (Lond.) 232:
- 109. Mocarelli, P., Marocchi, A., Brambilla, P., Gerthoux, P., Young, D. S., AND MANTEL, N.: Clinical laboratory manifestations of exposure to dioxin in children: a six-year study of the effects of an environmental
- disaster near Seveso, Italy. J. Am. Med. Assoc. 256: 2687-2695, 1986. 110. Moses, M., Lilis, R., Crow, K. D., Thornton, J., Fischbein, A., An-DERSON, H. A., AND SELIKOFF, I. J.: Health status of workers with past exposure to 2,3,7,8-tetrachlorodibenzo-p-dioxin in the manufacture of 2,4,5-trichlorophenoxyacetic acid: comparison of findings with and without chloracne. Am. J. Indust. Med. 5: 161-182, 1984.
- Neal, R. A., Olson, J. R., Gasiewicz, T. A., and Geiger, L. E.: The toxicokinetics of 2,3,7,8-tetrachlorodibenzo-p-dioxin in mammalian systems. Drug Metab. Rev. 13: 355-385, 1982.
- 112. NEBERT, D. W., AND GELBOIN, H. V.: Substrate-inducible microsomal aryl hydroxylase in mammalian cell culture. Assay and properties of induced
- enzyme, J. Biol. Chem. 243: 6242-6249, 1968. 113. Nebert, D. W., Goujan, F. M., and Gielen, J. E.: Aryl hydrocarbon hydroxylase induction by polycyclic hydrocarbons: simple autosomal dominant trait in the mouse. Nature New Biol. 236: 107–110, 1972.
- 114. NELSON, W. G., PIENTA, K. J., BARRACK, E. R., AND COFFEY, D. S.: The role of the nuclear matrix in the organization and function of DNA. Annu. Rev. Biophys. Biophys. Chem. 15: 457-475, 1986.
- 115. NEUHOLD, L. A., GONZALEZ, F. J., JAISWAL, A. K., AND NEBERT, D. W.: Dioxin-inducible enhancer region upstream from the mouse P₁-450 gene

- and interaction with a heterologous promoter. DNA (NY) 5: 403-411, 1986
- 116. OKEY, A. B., BONDY, G. P., MASON, M. E., KAHL, G. S., EISEN, H. J., GUENTHNER, T. M., AND NEBERT, D. W.: Regulatory gene product of the Ah locus. Characterization of the cytosolic inducer-receptor complex and evidence for its nuclear translocation. J. Biol. Chem. 254: 11636-11648. 1979.
- 117. OKEY, A. B., BONDY, G. P., MASON, M. E., NEBERT, D. W., FORSTER-GIBSON, C. J., MUNCAN, J., AND DUFRESNE, M. J.: Temperature-dependent cytosol-to-nucleus translocation of the Ah receptor for 2,3,7,8-tetrachlorodibenzo-p-dioxin in continuous cell culture lines. J. Biol. Chem. **255:** 11415–11422, 1980.
- 118. OKEY, A. B., DUBÉ, A. W., AND VELLA, L. M.: Binding of benzo(a)pyrene and dibenz(a,h)anthracene to the Ah receptor in mouse and rat hepatic cytosols. Cancer Res. 44: 1426-1432, 1984.
- 119. OKEY, A. B., MASON, M. E., GEHLY, E. B., HEIDELBERGER, C., MUNCAN. J., AND DUFRESNE, M. J.: Defective binding of 3-methylcholanthrene to the Ah receptor within C3H/10T1/2 clone 8 mouse fibroblasts in culture.
- Eur. J. Biochem. 132: 219-227, 1983.
 120. OKEY, A. B., AND VELLA, L. M.: Elevated binding of 2,3,7,8-tetrachlorodibenzo-p-dioxin and 3-methylcholanthrene to the Ah receptor in hepatic cytosols from phenobarbital-treated rats and mice. Biochem. Pharmacol. 33: 531-538, 1984.
- 121. OKRET, S., POELLINGER, L., DONG, Y., AND GUSTAFSSON, J. A.: Downregulation of glucocorticoid receptor in RNA by glucocorticoid hormones and recognition by the receptor of a specific binding sequence within a receptor cDNA clone. Proc. Natl. Acad. Sci. USA 83: 5899-5903, 1986.
- 122. OSBORNE, R., AND GREENLEE, W. F.: 2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD) enhances terminal differentiation of cultured human epidermal cells. Toxicol. Appl. Pharmacol. 77: 434-443, 1985.
- 123. PATTERSON, D. G., HOFFMAN, R. E., NEEDHAM, L. L., ROBERTS, D. W., BAGBY, J. R., PIRCKLE, J. L., FALK, H., SAMPSON, E. J., AND HOUK, V. N.: 2,3,7,8-Tetrachlorodibenzo-p-dioxin levels in adipose tissue of exposed and control persons in Missouri: an interim report. J. Am. Med. Assoc. 256: 2683-2686, 1986.
- 124. PEDERSON, D. S., THOMA, F., AND SIMPSON, R. T.: Core particle, fiber, and transcriptionally-active chromatin structure. Annu. Rev. Cell Biol. 2: 117-147, 1986
- 125. Peters, N. K., Frost, J. W., and Long, S. R.: A plant flavone, luteolin, induces expression of Rhizobium meliloti nodulation. Science (Wash. DC) **233:** 977-980, 1986.
- 126. PETERSON, C. L., ORTH, K., AND CALAME, K. L.: Binding in vitro of multiple cellular proteins to immunoglobulin heavy-chain enhancer DNA. Mol. Cell. Biol. 6: 4168–4178, 1986.
- 127. POELLINGER, L., LUND, J., DAHLBERG, E., AND GUSTAFSSON, J. A.: A hydroxylapatite microassay for receptor binding of 2,3,7,8-tetrachlorodibenzo-p-dioxin and 3-methylcholanthrene in various target tissues. Anal.
- Biochem. 144: 371-384, 1985.

 128. POELLINGER, L., LUND, J., GILLNER, M., AND GUSTAFSSON, J. A.: The receptor for 2,3,7,8-tetrachlorodibenzo-p-dioxin: similarities and dissimilarities with steroid hormone receptors. In Molecular Mechanism of Steroid Hormone Action, ed. by V. K. Moudgil, pp. 755-789, Walter de Gruyter and Co., Berlin, 1985.
- 129. POELLINGER, L., LUND, J., GILLNER, M., HANSSON, L. A., AND GUSTAFS-SON, J. A.: Physicochemical characterization of specific and nonspecific polyaromatic hydrocarbon binders in rat and mouse liver cytosol. J. Biol. Chem. **258**: 13535-13542, 1983.
- 130. Poiger, H., and Schlatter, C.: Pharmacokinetics of 2,3,7,8-TCDD in
- man. Chemosphere 15: 1489-1494, 1986.

 131. POLAND, A., AND GLOVER, E.: 2,3,7,8-Tetrachlorodibenzo-p-dioxin: a potent inducer of δ-aminolevulinic acid synthetase. Science (Wash. DC) 179: 476-477, 1973.
- 132. POLAND, A., AND GLOVER, E.: Chlorinated dibenzo-p-dioxins: potent inducers of δ -aminolevulinic acid synthetase and aryl hydrocarbon hydroxylase. Mol. Pharmacol. 9: 736-747, 1973.
- 133. Poland, A., and Glover, E.: Comparison of 2,3,7,8-tetrachlorodibenzo-pdioxin, a potent inducer of aryl hydrocarbon hydroxylase, with 3-methyl-
- cholanthrene. Mol. Pharmacol. 10: 349-359, 1974.
 134. POLAND, A., AND GLOVER, E.: Genetic expression of aryl hydrocarbon hydroxylase by 2,3,7,8-tetrachlorodibenzo-p-dioxin: evidence for a receptor mutation in genetically non-responsive mice. Mol. Pharmacol. 11: 389-398, 1975.
- 135. POLAND, A., GLOVER, E., EBETINO, F. H., AND KENDE, A. S.: Photoaffinity labelling of the Ah receptor. J. Biol. Chem. 261: 6352-6365, 1986.
- POLAND, A., GLOVER, E., AND KENDE, A. S.: Stereospecific, high affinity binding of 2,3,7,8-tetrachlorodibenzo-p-dioxin by hepatic cytosol. J. Biol. Chem. 251: 4936-4946, 1976.
- 137. POLAND, A. P., GLOVER, E., ROBINSON, J. R., AND NEBERT, D. W.: Genetic expression of aryl hydrocarbon hydroxylase activity. Induction of monooxygenase activities and cytochrome P1-450 formation by 2,3,7,8-tetrachlorodibenzo-p-dioxin in mice genetically "nonresponsive" to other aromatic hydrocarbons. J. Biol. Chem. 249: 5599-5606, 1974.
- 138. POLAND, A., GREENLEE, W. F., AND KENDE, A. S.: Studies on the mechanism of action of the chlorinated dibenzo-p-dioxins and related compounds. Ann. NY Acad. Sci. 320: 214-230, 1979.

(

- 139. POLAND, A., AND KIMBROUGH, R. D. (EDS.): Biological Mechanisms of Dioxin Action, 500 pp., Cold Spring Harbor Laboratory, Cold Spring Harbor, NY, 1984.
- 140. POLAND, A., AND KMUTSON, J. C.: 2,3,7,8-Tetrachlorodibenzo-p-dioxin and related halogenated aromatic hydrocarbons: examination of the mechanism of toxicity. Annu. Rev. Pharmacol. Toxicol. 22: 517-554, 1982.
- POLAND, A., PALEN, D., AND GLOVER, E.: Tumor promotion by TCDD in skin of HRS/J hairless mice. Nature (Lond.) 300: 271-273, 1982.
- 142. PTASHNE, M.: Gene regulation by proteins acting nearby and at a distance. Nature (Lond.) 322: 697-701, 1986.
- 143. RAPPE, C.: Chemical background of the phenoxy acids and dioxins. Ecol. Bull. 27: 28-30, 1978.
- 144. REDMOND, J. W., BATLEY, M., DJORDJEVIC, M. A., INNES, R. W., KUEM-PEL, P. L., AND ROLFE, B. G.: Flavones induce expression of nodulation genes in Rhizobium. Nature (Lond.) 323: 632-635, 1986.
- 145. RICE, R. H., AND CLINE, P. R.: Opposing effects of 2,3,7,8-tetrachlorodibenzo p-dioxin and hydrocortisone on growth and differentiation of cultured malignant human keratinocytes. Carcinogenesis (Lond.) 5: 367-371, 1984.
- 146. RINGOLD, G. M.: Steroid hormone regulation of gene expression. Annu. Rev. Pharmacol. Toxicol. 25: 529-566, 1985.
- 147. ROBERTSON, J. A., CHEN, H. C., AND NEBERT, D. W.: NAD(P)H:menadione oxidoreductase: novel purification of enzyme, cDNA and complete amino acid sequence, and gene regulation. J. Biol. Chem. 261: 15794-15799, 1986.
- 148. ROBINSON, J. R., CONSODINE, N., AND NEBERT, D. W.: Genetic expression of ary hydrocarbon hydroxylase induction. Evidence for the involvement of other genetic loci. J. Biol. Chem. 249: 5851-5859, 1974.
- 149. ROSENFELD, P. J., AND KELLY, T. J.: Purification of nuclear factor I by DNA recognition site affinity chromatography. J. Biol. Chem. 261: 1398-1403, 1986.
- 150. SAFE, S. H.: Comparative toxicology and mechanism of action of polychlorinated dibenzo-p-dioxins and dibenzofurans. Annu. Rev. Pharmacol. Toxicol. 26: 371-399, 1986.
- 151. SASSONE-CORSI, P., DOUGHERTY, J. P., WASYLYK, B., AND CHAMBON, P.: Stimulation of in vitro transcription from heterologous promoters by the
- SV40 enhancer. Proc. Natl. Acad. Sci. USA 81: 308-312, 1984. 152. SCHMID, F. A., ELMER, I., AND TARNOWSKI, G. S.: Genetic determination of differential inflammatory reactivity and subcutaneous tumor susceptibility of AKR/J and C57BL/6J mice to 7,12-dimethylbenz(a)anthracene.
- Cancer Res. 29: 1585-1599, 1969.
 153. SCHMIDT, T. J., DIEHL, E. E., DAVIDSON, C. J., PUK, M. J., WEBB, M. L. AND LITWACK, G.: Effects of pancreatic ribonuclease A, S protein, and S peptide on activation of purified rat hepatic glucocorticoid-receptor complexes. Biochemistry 25: 5955-5961, 1986.
- 154. SCHMIDT, T. J., MILLER-DIENER, A., WEBB, M. L., AND LITWACK, G.: Thermal activation of the purified rat hepatic glucocorticoid receptor. Evidence for a two-step mechanism. J. Biol. Chem. 260: 16255-16262, 1985.
- 155. SEN, R., AND BALTIMORE, D.: Multiple nuclear factors interact with the immunoglobulin enhancer sequences. Cell 46: 705-716, 1986.
- 156. SERFLING, E., JASIU, M., AND SCHAFFNER, W.: Enhancers and eukaryotic gene transcription. Trends Genet. 1: 224-230, 1985.
- 157. SLOOP, T. C., AND LUCIER, G. W.: Dose-dependent elevation of Ah receptor binding by TCDD in rat liver. Toxicol. Appl. Pharmacol., in press, 1987.
- 158. SMITH, A. C., ELSASSER, M. S., AND HARMON, J. M.: Analysis of glucocorticoid receptor activation by high resolution two-dimensional electrophoresis of affinity-labeled receptor. J. Biol. Chem. 261: 13285-13292, 1986.
- 159. Sogawa, K., Fujisawa-Sehara, A., Yamane, M., and Fujii-Kuriyama, Y.: Location of regulatory elements responsible for drug induction in the rat cytochrome P-450c gene. Proc. Natl. Acad. Sci. USA 83: 8044-8048,

- 160. Sparschu, G. L., Dunn, F. L., and Rowe, V. K.: Study of the teratogenicity of 2,3,7,8-tetrachlorodibenzo-p-dioxin in the rat. Food Cosmet. Toxicol. 9: 405-412, 1971.
- 161. Suskind, R. R., and Hertzberg, V. S.: Human health effects of 2,4,5-T and its toxic contaminants. J. Am. Med. Assoc. 251: 2372-2380, 1984.
- 162. Takahashi, K., Vigneron, M., Matthes, H., Wildeman, A., Zenke, M., AND CHAMBON, P.: Requirement of stereospecific alignments for initiation from the simian virus 40 early promoter. Nature (Lond.) 319: 121-126, 1986.
- 163. Thomas, P. E., and Hutton, J. J.: Genetics of aryl hydrocarbon hydroxylase induction: additive inheritance in crosses between C3H/HeJ and DBA/2J. Biochem. Genet. 8: 249-257, 1973.
- 164. THOMAS, P. E., KOURI, R. E., AND HUTTON, J. J.: The genetics of arvl hydrocarbon hydroxylase induction in mice: a single gene difference between C57BL/6J and DBA/2J. Biochem. Genet. 6: 157-168, 1972.
- 165. Tierney, B., Weaver, D., Heintz, N. H., Schaffer, W. I., and Bresnick, E.: The identity and nuclear uptake of a cytosolic binding protein for 3methylcholanthrene. Biochim. Biophys. Acta 200: 513-523, 1980.
- 166. TSUI, H. W., AND OKEY, A. B.: Rapid vertical tube rotor gradient assay for binding of 2,3,7,8-tetrachlorodibenzo-p-dioxin to the Ah receptor. Can J Physiol. Pharmacol. 59: 927-931, 1981.
- 167. VAN GURP, J. R., AND HANKINSON, O.: Isolation and characterization of revertants from four different classes of aryl hydrocarbon hydroxylasedeficient Hepa-1 mutants. Mol. Cell. Biol. 4: 1597-1604, 1984.
- 168. WATERMAN, M. R., AND SIMPSON, E. R.: Regulation of the synthesis of cytochromes P-450 involved in steroid hormone synthesis. Mol. Cell. Endocrinol. 39: 81-89, 1985.
- WEINTRAUB, H.: Assembly and propagation of repressed and derepressed chromosomal states. Cell 42: 705-711, 1985.
- 170. WEISBROD, S.: Active chromatin. Nature (Lond.) 297: 289-295, 1982.
- 171. WELSHONS, W. B., LIEBERMAN, M. B., AND GORSKI, J.: Nuclear localization of unoccupied oestrogen receptors. Nature (Lond.) 307: 747-749, 1984.
- 172. WHITESIDE, T.: Defoliation. The New Yorker 45: 32-69, 1970 (Feb. 7).
- 173. WHITLOCK, J. P., JR.: The regulation of cytochrome P-450 gene expression.
- Annu. Rev. Pharmacol. Toxicol. 26: 333-369, 1986. 174. WHITLOCK, J. P., JR., AND GALEAZZI, D. R.: 2,3,7,8-Tetrachlorodibenzo-pdioxin receptors in wild type and variant mouse hepatoma cells. Nuclear location and strength of nuclear binding. J. Biol. Chem. 259: 980-985. 1984
- 175. WILHELMSSON, A., WIKSTROM, A. C., AND POELLINGER, L.: Polyanionicbinding properties of the receptor for 2,3,7,8-tetrachlorodibenzo-p-dioxin: a comparison with the glucocorticoid receptor. J. Biol. Chem. 261: 13456-13463, 1986.
- 176. WILLIAMS, J. B., Lu, A. Y. N., CAMERON, R. G., AND PICKETT, C. B.: Rat liver NAD(P)H:quinone reductase: construction of a quinone reductase cDNA clone and regulation of quinone reductase mRNA by 3-methylcholanthrene and in persistent hepatocyte nodules induced by chemical carcinogens. J. Biol. Chem. **261**: 5524-5528, 1986.
- 177. WOLFF, M. E., BANTER, J. D., KOLLMAN, P. A., LEE, D. L., KUNTZ, K. D., BLOOM, E., MATULICH, D. T., AND MORRIS, J.: Nature of steroidglucocorticoid receptor interactions: thermodynamic analysis of the binding reaction. Biochemistry 17: 3201-3208, 1978.
- YAMAMOTO, K. R.: Steroid receptor regulated transcription of specific genes and gene networks. Annu. Rev. Genet. 19: 209-252, 1985.
 YAMAMOTO, K. R., GEHRING, U., STAMPFER, M. R., AND SIBLEY, C. H.:
- Genetic approaches to steroid hormone action. Recent Prog. Horm. Res. **32:** 3-32, 1976.
- 180. ZACK, J. A., AND SUSKIND, R. R.: The mortality experience of workers exposed to tetrachlorodibenzodioxin in a trichlorophenol process accident.
- J. Occup. Med. 22: 11-14, 1980.
 181. ZYTKOVICZ, T. H.: Identification and characterization of a high-affinity saturable binding protein for the carcinogen benzo(a)pyrene. Cancer Res. 42: 4387-4393, 1982.

Research News

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Dioxin Risks Revisited

Armed with a new understanding of how dioxin works on the molecular level, a number of scientists are challenging EPA to change the way it does risk assessment

WHEN A DISPARATE GROUP OF 38 REsearchers and regulators from the United States and Europe got together at a recent meeting on dioxin, they reached an agreement that surprised almost everyone. At the Banbury Center at Cold Spring Harbor Laboratory, they agreed that before dioxin can cause any of its myriad toxic effects, be they cancer or birth defects, it must first bind to and activate a receptor. And this unlikely agreement on how dioxin works at the molecular level-and some hurried calculations scribbled on a blackboard-could force a dramatic change in how the federal government assesses the risk of this and similar carcinogens.

After the decades of scientific debate that have dogged this chemical, consensus on anything seems surprising. Scientists have been struggling to figure out just how dangerous dioxin really is ever since it was first detected in the late 1950s as a by-product of herbicide manufacture. Animal studies have shown this ubiquitous pollutant to be exquisitely lethal, the most potent carcinogen ever tested. But human effects have been notoriously difficult to pin down, as shown by the decades-long controversy over the dioxin-tainted defoliant Agent Orange. Even among highly exposed groups, like the people who lived near the chemical plant that exploded in Seveso, Italy, in 1976, the only undisputed effect until recently has been the skin disease chloracne. Just last month, however, a new epidemiologic study provided what may be the strongest link yet between high doses of dioxin and human cancer (see boxes on pp. 625 and 626).

In the absence of definitive human data, the Environmental Protection Agency has assumed the worst, adopting a linear risk assessment model that posits that there is no safe level of dioxin and that its toxic effects rise proportionately with dose. EPA then set a stringent acceptable intake level at 0.006 picograms per kilogram of body weight per day. By contrast, Canada and some European countries, which dismissed the linear model as unrealistic, have set their limits about 170 to 1700 times higher than EPA's, at 1 to 10 picograms per kilogram per day. Yet, sighs toxicologist Michael Gallo of the Robert Wood Johnson Medical School in

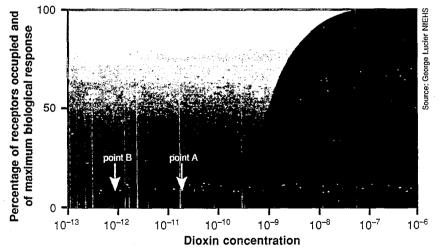
New Jersey, "It's the same chemical on both sides of the Atlantic."

Now comes the Banbury Center meeting. Organized by Gallo, Robert Scheuplein of the Food and Drug Administration, and Cornelius van der Heijden of the National Institute for Public Health in the Netherlands, it suddenly offered a way out of the morass. If receptor binding is indeed the essential first step before any toxic effects can occur, as the meeting participants agreed, then that implies there is a "safe" dose or practical "threshold" below which no toxic effects occur. And that, in turn, means that the model EPA uses is wrong. "It topples the linear multistage model," exclaims Gallo.

Spurred on by the Banbury meeting, Gallo and others are now urging EPA and the other federal agencies to abandon that will also be applicable to other carcinogens that work through receptors. "This is bigger than dioxin."

EPA scientist Linda Birnbaum, director of the environmental toxicology division of EPA's Health Effects Research Laboratory in North Carolina, is no less enthusiastic. "It's a new way to do risk assessment. We can set a limit below which there cannot be an effect, on a mechanistic basis. Instead of saying we know nothing and have to extrapolate back to zero, we are saying we know a hell of a lot and can make predictions."

But everything about dioxin is contentious, and the Banbury meeting sparked its own share of dispute. Consensus broke down on just what such a receptor-based model would predict in terms of dioxin's danger. Gallo and Scheuplein contend that the new



A dioxin receptor model. New findings suggest that responses to dioxin increase slowly at first but then shoot up after passing a critical concentration.

model, which they use as a "default" model for lack of a better alternative, and try to predict dioxin's risk based on a molecular understanding of how the chemical works. When EPA regulators adopted the default model for carcinogens in the late 1970s, their intention was always to replace it with something more appropriate—once they knew enough to do so. But that has rarely happened. "If we can't do it for dioxin, for which we have so much information, then we probably can't do it for anything," says Gallo, who thinks that this new approach

model will show dioxin to be far less risky than U.S. agencies now calculate. Others, like George Lucier of the National Institute for Environmental Health Sciences (NIEHS) in North Carolina, say such speculation is premature. And Ellen Silbergeld, a toxicologist formerly with the Environmental Defense Fund and now at the University of Maryland, thinks speculation that dioxin is less risky may be dead wrong.

And even if the new model does indicate that EPA's risk number is far too conservative, revising it would be horrendously dif-

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ficult-especially for a molecule as politically charged as dioxin. Gallo calls the substance a powerful "litigen," referring to the scores of lawsuits that have been filed by people alleging health effects from environmental exposure to dioxin. Michael Gough of the Office of Technology Assessment and author of Dioxin: Agent Orange predicts "a tremendous uproar from environmental groups and Congress." Indeed, John Moore tried to revise both the dioxin risk number and the model during his tenure as assistant administrator for pesticides and toxic substances at El'A. He was foiled both times, essentially because the scientific rationale wasn't strong enough.

Now it may be, thanks largely to the Banbury meeting, says Moore, who now heads the Institute for Evaluating Health Risks in Irvine. What tipped the scale is not so much new experimental data as the accumulating weight of evidence. Indeed, awareness that dioxin binds to a specific receptor, known as the Ah, or aromatic hydrocarbon receptor, goes back to work done in the 1970s by Alan Poland of the University of Wisconsin. Since then, the nagging question has been whether all of dioxin's effects—including cancer—are mediated through the receptor.

That question was at last laid to rest at Banbury. When researchers pooled their data, they realized that for every effect studied so far, in every experimental system, binding to the receptor was the first and essential step. Indeed, no effect can occur until the receptor-dioxin complex is activated and transported to the cell nucleus, where it interacts with the DNA and sets off a cascade of events. Poland cautions, however, that someone may yet turn up an effect that is not mediated this way.

What's more, says Gallo, drawing on classic receptor-occupancy theory, several thousand of the receptors have to be occupied before any biological response is seenthough the exact number is a matter of considerable controversy. To Birnbaum of EPA, "The key point is that there is a dose of dioxin below which the receptor does not function, and if it is not activated, there can be no effect," though she and others shy away from saving there is a threshold in the strict sense. The upshot, most but not all of the Banbury participants agreed, is that the straight line predicted by the linear multistage model is wrong. Instead, the curve at its lower end looks like a hockey stick in which the response increases very slightly at low doses, along the blade, and then shoots up almost linearly at the bend in the stick.

The key question, then, is where the response shoots up in humans, which the group set our to determine in a flurry of

High Dioxin Dose Linked to Cancer

For two decades now a debate has been raging about whether dioxin causes cancer in humans. Animal studies have shown one form of dioxin, TCDD, to be the most powerful carcinogen ever tested, earning it a reputation as a pariah, the Darth Vader of chemicals. But human epidemiologic studies, which have been hampered by insufficient exposure data or small numbers, have been equivocal. Over the past few years a "revisionist" school has emerged, asserting that, in the absence of any definitive cancer link in humans, dioxin must have been given a bum rap. Now, a new study by federal scientists presents what many consider the strongest evidence yet that dioxin is indeed a human carcinogen—but apparently only at exceedingly high doses. In an editorial accompanying the study, which was published in the 24 January issue of The New



Dioxin sleuth. Marilyn Fingerhut ran NIOSH study.

England Journal of Medicine, biostatistician John Bailar III of McGill University in Montreal calls it "a model of its kind. We are likely to wait a long time for appreciably better or broader evidence of the effects of TCDD on human health."

In the exhaustive study, which took nearly 13 years to complete, Marilyn Fingerhut and her colleagues at the National Institute for Occupational Safety and Health examined the mortality records of essentially all U.S. chemical workers exposed to dioxin on the job from 1942 to 1984: a total of 5172 men at 12 different plants. What sets the study apart, other than its size, is that this is probably the most highly exposed population ever studied, says Fingerhut. What's more, their exposure was well characterized. The NIOSH team measured TCDD levels in the blood serum of 253 of the workers. The result: the levels correlated well with their surrogate measure, which was how long a worker was in a dioxin-contaminated job.

The workers overall had a 15% increase in mortality from all cancers. But that picture changed dramatically once the cohort was divided into a low-exposure and a high-exposure group. Low exposure was defined as working less than I year in a dioxin-contaminated job; high exposure as 1 year or more. The men in both groups had their first occupational exposure to dioxin at least 20 years earlier, allowing for a 20-year latency period for cancer. In the low-exposure group, there was no increased risk of cancer, even though those men were exposed to dioxin levels an estimated 90 times higher than the general population. By contrast, the highexposure group, who received doses estimated to be 500 times higher than the general population's, had an almost 50% excess risk of dying of cancer. The increase was mostly in soft tissue sarcomas, a form of cancer linked to dioxin in other epidemiologic studies. But there was also an unexpected increase in cancers of the respiratory system. The study did not show a significant increase in the handful of other cancers that have been linked to dioxin in epidemiologic studies. "Even a study this large, with all the workers in the U.S., has limitations in size for looking at individual cancers," explains Fingerhut.

The study has other limitations as well. For one, workers were exposed to other occupational chemicals, often for 20 years, and the epidemiologists could not control for their effects. Nor could they control for smoking. Fingerhut thinks neither factor is likely to explain the excess cancer risk, but she cannot definitively rule out that possibility. Nevertheless, she sees the study's outcome as very clear, writing: "The increased mortality is consistent with the status of TCDD as a carcinogen." This study probably defines the upper end of human effects, adds Fingerhut, who leaves it to others to speculate about what it means for people exposed to lower doses of dioxin.

Will this study settle the dioxin controversy? Not likely, if newspaper headlines are any indication. "Extensive Study Finds Reduced Dioxin Danger," heralded *The Washington Post*. "High Dioxin Levels Linked to Cancer," warned *The New York Times*. And the study is already being cited as evidence in the flap over Monsanto's alleged falsification of its dioxin studies (see box on p. 626). Indeed, Bailar predicted that "parties on both sides of the continuing debate about the regulation of dioxin exposure will no doubt cite this work in support of their positions."

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excitement on the last day of the meeting. Instead of direct measures of receptor binding, they used a handy surrogate: the increased activity of the cytochrome P450 enzyme system, widely considered the most sensitive response to dioxin in all species. No toxic effects are known to occur at levels below those required for enzyme induction.

After reviewing data on the necessary dose for enzyme induction in all species, Gallo, Birnbaum, Scheuplein, and others took turns at the blackboard, trying to calculate what the "safe" level in humans might be. Their rough, back-of-the-envelope calculation: I to 3 picograms per kilogram per day—several hundred times higher than current U.S. standards and in the same ballpark as those set by some European countries, which arrived there by an entirely different method.

Not so fast, says Maryland's Silbergeld, who cautions against "replacing one stupid model with another." For one, a receptor-based model does not necessarily predict a

"hockey stick" curve, nor does receptor binding necessarily imply a "safe" dose, says Silbergeld, who thinks her colleagues are underestimating the intricacies of receptor theory. Nor is she convinced "that the result [of the new model] will be that different from EPA's current figure. As a scientist, I object to the EPA model. But [its predictions] may be very, very close, for totally irrelevant reasons."

Working with EPA scientists, Gallo is now setting out to refine the risk number for dioxin. George Lucier and his colleagues at NIEHS are doing the same. The idea is to build a conceptual model of cellular responses to dioxin and then turn that over to mathematicians to develop a predictive tool to estimate dioxin's risks—not just for cancer but for any toxic endpoint. William Farland, who runs the dioxin risk assessment effort at EPA, expects a "straw man" model to be complete in about a year. The next step would be to see if it passes muster with the

scientific community—and if it in fact offers an advantage over the status quo. "This is an improvement, not a cure-all," warns Lucier.

Once the model is complete, perhaps the biggest question, in terms of dioxin's danger, is the background exposure of the general population, which comes chiefly from diet but also from environmental sources. If background exposure is comfortably below the practical "threshold" needed for receptor activation (point B in the figure), then there may indeed be a safe dose. But if background exposure is higher, near the "threshold" (point A), "then there is no margin for additional exposure," says Moore. Background exposure is now estimated to be about 1 picogram per kilogram per day-slightly below the rough "safe" number the Banbury group came up with-which may not leave much room for additional exposure.

At this juncture, EPA officials are enthusiastically embracing the new scientific approach. Don Barnes, a dioxin expert and executive director of EPA's Scientific Advisory Board, talks of "a real breakthrough, a sea change in our view of dioxin." In fact, the topic is deemed important enough that a special briefing is planned for EPA administrator William Reilly and top agency officials.

But how far is EPA likely to go if the modeling exercise does reveal that dioxin is less risky than the agencies now calculate? Gough of OTA, for one, thinks that the answer is not very far: "Dioxin is the most potent carcinogen ever tested. If they back off this one, they will open the door to every chemical manufacturer in the world" whose chemical acts in the same way. "That is a door they will reluctantly open." Gallo contends that the door will open just a crack, as there are less than a dozen carcinogens known to work the way dioxin does. And he predicts that the new receptor-based risk model will cut both ways: some carcinogens will turn out to be far riskier than now predicted; others, like dioxin, less risky.

Moore agrees that change will not be easy. "For issues this emotional, you have to be purer than Caesar's wife anytime you propose to change the status quo. There would have to be a fair degree of support within the scientific community for it to come to pass, especially if the potential change is a 'relaxing' of the number."

Eric Bretthauer, EPA's assistant administrator for research and development, concedes that "the agency hasn't traditionally relaxed numbers." But, he says, "I think there is a willingness at the policy level to take it on. My view is we have to be open to changes in science, whatever their effect on regulatory policy." He adds, however, that "the science has to be very clear."

■ LESLIE ROBERTS

Monsanto Studies Under Fire

The Environmental Protection Agency has launched a criminal investigation to determine whether Monsanto Corp. of St. Louis falsified three epidemiologic studies of its workers, which showed no increased health risks from dioxin other than the skin disease chloracne. The investigation, which EPA is mandated to conduct in response to a petition requesting it from the activist group Greenpeace USA, should resolve, once and for all, the allegations that have been swirling around these studies for almost a year. EPA officials would not confirm or deny the existence of the investigation, but *Science* obtained internal agency memos discussing it.

The EPA has not notified Monsanto that it is under investigation, but says Dan Bishop, the company's director of communications, "We hope there is one, we welcome it. It is the only way to put this matter to rest." In fact, the company wrote to EPA twice over the past few months, begging the agency to perform a scientific audit of the studies. Bishop calls the fraud allegations "bald-faced lies."

The main charges are that Monsanto epidemiologists misclassified exposed workers as unexposed in their control group and that they omitted workers who had died of two cancers that have been linked to dioxin exposure in other epidemiologic studies. The charges first came to light last February when a plantiff's lawyer in Kemner v. Monsanto, a case involving a tank-car accident, reviewed the studies, decided they were fraudulent, and alerted the press to the alleged cover-up. That brought in Greenpeace, and also Cate Jenkins, a chemist in EPA's regulatory branch. She has since made the Monsanto studies something of a personal crusade, petitioning EPA's Science Advisory Board to audit these and other studies, and meanwhile sending numerous copies of her memos to various environmental groups, Vietnam veterans organizations, and her friends on Capitol Hill. Jenkins maintains that Monsanto's studies have directly affected how EPA regulates dioxin. Other agency officials deny that, saying that EPA's current—and very stringent—standard for dioxin exposure is based on animal studies.

Everyone Science spoke with who is familiar with the Monsanto studies agrees that they are flawed, but probably not as the result of criminal intent. The scientific questions about the studies may now be moot, however, as all but six of the Monsanto workers in the three studies have been carefully reexamined as part of a larger federal study just published, which suggests that high dioxin doses can cause human cancer (see box on page 625). The other questions may be tougher to resolve. When EPA completes its investigation, the agency will report to the Justice Department and recommend either that they prosecute or close the case.

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LEAD TOXICITY

Case study for short course on Risk Analysis in Occupational and Environmental Health

School of Public Health Harvard University

September 4-6, 1991

Lead has been chosen for a case study, because it brings out a lot of different issues related to risk analysis. Moreover it is a problem of active interest at the present time.

Lead acetate has been shown to be carcinogenic in animals, but lead acetate is not usually the form in which humans are exposed. An exception is the men's hair dye GRECIAN FORMULA which consists of lead acetate, but risk analyses both by the manufacturer and by FDA have shown that normal application to the scalp produces risks of less than one in a million per lifetime. It will not therefore be of concern to us here.

EXPOSURE

There are several exposure routes:

- (1) Dermal application of lead acetate as a hair dye
- (2) Ingestion of lead from
 - (i) water from lead pipes
 - (ii) water from pipes soldered with lead solder
 - (iii) eating from lead glazed dishes
 - (iv) eating vegetables grown in soil containing lead
 - (v) leaching of lead from crystal and plastic food bags
- (3) Childhood ingestion of (i) peeling lead paint
 - (ii) house dust from lead paint
 - (iii) lead from soil
- (4) Inhalation of lead oxide (i) from combusted leaded gasoline (ii) from suspended soil dust
- (5) Inhaled/ingested lead from home renovation/paint stripping and welding/soldering.

The calculation of <u>exposure</u> in environmental cases is often complex and fraught with approximations and possibly errors. Whenever the <u>dose</u> can be measured directly, it is clearly superior to using a complex calculation of exposure and deriving the dose. Lead has appeared in the blood, and blood lead measurements can be and have been made. The averaging time for blood lead measurements is not completely known but it is longer than a day, and shorter than a lifetime. Dentine (tooth) lead and bone lead levels have often been taken and are regarded to be superior when available. Blood lead levels can either be taken by themselves, or as calibrations for the complex exposure calculations.

Today's major concerns are the neurobehavioral effects on children and blood pressure effects on adults. At the turn of the century, levels of lead in the blood averaged 30 $\mu g/dl$ in major cities, and often exceeded 100 $\mu g/dl$. There were many cases of overt toxicity. Now the concentrations are down in the range 5 to 20 $\mu g/dl$, the question arises: are there non-overt cases of intoxication? Is there a threshold for such effects? and what are the effects on public health as a whole?

It is these questions that we ask you to think about.

Questions for consideration during the course

The carcinogenicity of organic compounds is considered for each compound separately. For example, chlorine by itself is not considered to be a carcinogen, but many chlorinated organic compounds are. Does the same rationale apply to inorganic compounds? Should we regard all lead compounds as carcinogenic because lead acetate is?

What are the requirements for a direct dose measurement? Why is not presence in urine usually considered a good indicator of dose? Is it a good indicator of exposure?

What would be the best marker for cumulative lead exposure?

Should we be more or less careful in our (a) calculations (b) regulatory criteria because we have a more direct dose measurement than for most pollutants?

Is it likely that there is a linear dose response relationship for effects of lead on:

- (i) IQ?
- (ii) neurobehavioral development?
- (iii) blood pressure?

Several people have found that blood lead does not increase proportionally with soil lead above 2000 ppm in soil. What are the implications for a dose response relationship?

There is a statistical reverse correlation of IQ with blood lead. What is the direction of causality? Does eating lead paint cause low IQ? Or do people with low IQ live in houses where the children eat lead paint? How can one tell?

What are the public health implications of a 4 point reduction of IQ with levels of lead at 40 $\mu g/dl$? Of two 3 point increase in blood pressure of 40 $\mu g/dl$?

The average blood lead seems to have fallen from 30 $\mu g/dl$ in 1990 to below 10 today:

- (i) What is/are the reason/s for the reduction?
- (ii) Is it low enough?
- (iii) How can one tell?
- (iv) If there are bad effects at 10 µg/dl why were they not overt at 30?

ATTACHMENTS

- (1) Toxicity profile for lead.
- (2) Paper: Lippmann, Morton. "Lead and Human Health: Background and Recent Findings". *Environmental Research*, <u>51</u>, pp. 1-24 (1990).
- (3) Paper: Silbergeld, E.K. "Lead in Bone: Implications for Toxicology during Pregnancy and Lactation". *Environmental Health Perspectives*, Vol. <u>91</u>, pp. 63-70 (1991).
- (4) Paper: Needleman, H.L. et al "The Long-Term Effects of Low Doses of Lead in Childhood". *The New England Journal of Medicine*, Vol. 322, No. 2, pp. 83-88 (1990).

CALCULATION FOR SOIL INGESTION

Factors to be measured

express results as:

Concentration of Pb in soil

Mean (Geometric) Deviation

Amount eaten by children

Mean (Geometric) Deviation

Absorption by gut (includes solubility)

Mean (Geometric) Deviation

Relationship of blood lead to gut absorption

The resultant blood level is the product of all 4 factors.

To the extent that the factors are independent, <u>and</u> the relationships are linear, the deviation of distribution of the blood lead is obtained by taking the root mean square of the deviations of the individual distributions.

Lead

CAS #7439-92-1 (1)

Molecular Weight: 207.2 (1)

Criteria and Standards

EPA Group B₂ Carcinogen

Cancer Potency Factor (CPF): None established due to uncertainty and importance of other health effects at low levels (2)

Reference Dose (RfD): No threshold level established, since very low levels are known to cause adverse health effects, especially in children. Current risk assessment methodology involves calculating the projected population distribution of blood lead levels associated with various exposure scenarios. (2) (15)

Maximum Contaminant Level Goal: 20 μg/l, proposed (drinking water) (2)

Maximum Contaminant Level: 50 μ g/l, pro: aulgated (drinking water) (2)

Ambient Water Quality Criteria: 50 μ g/l, based on ingesting aquatic organisms and drinking water (2)

Ambient Water Quality Criteria: 50 µg/l, adjusted for drinking water only (2)

Acute Intake Chronic: 1.4 x 10⁻³ mg/kg-day, oral (3)

 4.3×10^4 mg/kg-day, inhalation (3)

Health Advisory: 20 μ g/day (lifetime, drinking water) (3)

American Conference of Government Industrial Hygienists:

Threshold Limit Value-Time Weighed Average: 0.15 mg/m³, airborne inorganic dust and fumes, as Pb (4)

Centers for Disease Control:

Elevated Blood Lead Level for Children: 25 μ g/dl (associated with a blood erythrocyte protoporphyrin level of 35 μ g/dl or greater (11)

Chemistry and Uses

Lead is a heavy metal that exists in one of three oxidation states 0, +2, and +4. Metallic lead and common lead minerals are relatively insoluble in water, however, organic lead compounds are water soluble (5). Metallic lead is used as a major component of many alloys such as solder, print-type metal, and many bronzes. Lead compounds also have a wide variety of uses as paint pigments, in storage batteriesm, and in ceramics (1).

Pharmacokinetics

Approximately 8% of the lead ingested by human adults is thought to be absorbed. Absorption rates in children are higher, for example, children are thought to absorb as much as 45-50% of lead in foods (8). This absorption level is generally higher in animals or humans that have been fasting. The absorption rate for human infants is approximately 50%. Lead is also absorbed after inhalation; reported pulmonary deposition rates as range from 30% to 50%.

After being absorbed by the body, most lead compounds dissociate, yielding inorganic lead. Tetraethyl and tetramethyl leads are dealkylated to tri- and di- alkyl compounds which are more toxic than the parent compounds. In human adults, under conditions of long-term exposure, approximately 95% of the total amount of lead found in the body is localized in the skeleton. In the blood, most lead is found in the erythrocytes. Lead also readily crosses the placenta. In most species, the main route of excretion is through the bile. However, in baboons and humans, urine appears to be the primary route (5,8).

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Toxicity

Systemic Effects

Human

At high exposure levels, lead produces encephalopathy, gastrointestinal effects, anemia, nephropathy, and electrocardiographic abnormalities. These effects are primarily seen in acutely poisoned children or in adults from occupational exposures. Lower level exposure to lead in all humans can affect the synthesis of heme, which, in turn, affects metabolic processes and decreases vitamin D circulating in the body, reducing calcium stability in the body.

Inhalation of airborne lead is generally a minor exposure pathway for children, but ingestion of lead-containing particles in dust can contribute significantly to children's lead exposure (11). Effects of great concern from low level lead exposure include neurobehavioral decrement and growth retardation in infants exposed prenatally and children exposed postnatally. Based on blood lead concentrations, no clear threshold for neurobehavioral effects has been shown from low level lead exposures resulting in blood lead levels < 10-15 μ g/dl (9).

Increased blood pressure from low level lead exposure in middle aged men has been observed following low level lead exposures. An effects threshold for increased blood pressure in men has not been defined; several studies have failed to find one while one longitudinal study suggests of threshold of 30 μ g/dl (16).

Animal

In experimental animals, effects associated with exposure to lead and lead compounds are similar to those in humans. Observed effects have included weight loss, decreased survival, and neurological, cardiovascular, and kidney effects. Several studies with experimental animals suggest that lead may interfere with the immune response (5).

Carcinogenicity

Human

The EPA has classified lead as a Group B₂ Carcinogen. Data concerning the carcinogenicity of lead in humans are inconclusive. There is no evidence that oral exposure produces a tumor response. Although studies of occupational inhalation exposure have produced largely negative results, increases in cancer of the digestive organs, respiratory system and kidney have been reported (2,6,19)

Animal

There is evidence in experimental animals that lead salts are carcinogenic in both mice and rats, resulting in tumors of the kidneys after either oral or parenteral administration. Most of the investigations found a carcinogenic response only at the highest dose. It is unclear how this effect relates to the lower level exposures typical to humans. Metallic lead, lead oxide and lead tetralkyls have not been tested adequately. No studies are available on the carcinogenic potential of lead compounds via inhalation (2).

Mutagenicity

In a number of DNA structure and function assays, lead has been shown to affect the molecular processes associated with the regulation of gene expression. Lead acetate induces

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cell transformation in Syrian hamster embryo cells and enhances the incidence of simian adenovirus induction. Lead oxide demonstrates a similar enhanced adenovirus induction. Under certain conditions, lead compounds may induce chromosomal aberrations <u>in vivo</u> and in tissue cultures. One study showed a relationship between sister chromatid exchange and lead exposure in exposed workers (2).

Reproductive Effects

In experimental animals, various non-teratogenic reproductive effects have been observed including developmental delays, decreased fertility, and fetotoxicity. No reproductive effects from human oral exposure to lead have been reported; however, occupational inhalation exposures have been linked to altered testicular function, increases in spontaneous abortion, premature delivery, and early membrane rupture (5).

Basis for Lead Criteria

The classification of lead as B2, probable human carcinogen, is based on sufficient animal data and insufficient human data. Ten rat bioassays and one mouse assay showed statistically significant increases in renal tumors with dietary and subcutaneous exposure to several soluble lead salts. The most characteristic cancer response is bilateral renal carcinoma, however, there is some evidence of multiple tumor sites (2).

Cancer risk due to exposure to lead involves many uncertainties, such as age, health, nutritional state, body burden and exposure duration which influence the absorption, release and excretion of lead. In addition, current knowledge of lead pharmacokinetics indicates that an estimate derived by standard procedures would not truly describe the potential risk. Therefore, the EPA does not currently recommend a specific cancer potency factor (2).

The water quality criteria of maximum contaminant level goal (MCLG) is based on neurological effects of lead in infants and adverse effects associated with blood lead levels

of 15 μ g/dl. Using a conversion factor of 6.25 to convert from blood lead concentrations to drinking water lead concentrations and an uncertainty factor of 5, the MCLG of 20 μ g/l was proposed (2).

The Centers for Disease Control (CDC) has defined an elevated blood lead level for children, which reflects excessive absorption of lead, as a confirmed concentration of lead in whole blood of 25 μ g/dl or greater (11). This level is based on several studies. For example, a study of children living near a lead smelter found an erythrocyte protoporphyrin (EP) response at blood lead levels ranging between 10 and 20 μ g/dl. Although the biologic threshold for lead toxicity, based on an EP response, is thus less than 20 μ g/dl, CDC set the criteria for screening based on several additional factors including acceptability, cost-effectiveness, and the feasibility of effective intervention and follow-up. Thus, the CDC-recommended intervention lead level is 25 μ g/dl, associated with an EP level of 35 μ g/dl or greater. The CDC is currently reviewing the blood lead level of concern; the guideline is expected to be revised downward, but it is unclear whether CDC will consider the distinction between blood lead levels associated with prenatal, and, hence, maternal exposures and those associated with post-natal exposures. (17).

Risk characterization of lead exposure generally involves using mathematical models to predict blood lead levels that will result from any given range of lead uptake rates. These models allow blood lead levels to be related quantitatively to uptake rates and can provide estimates of the frequency distribution of blood lead levels associated with any given uptake lead exposure scenario.

The Integrated Uptake/Biokinetic (IU/BK) Model, developed for of the U.S. Environmental Protection Agency, accepts either monitoring data or estimated values for the levels of lead in various media. The model predicts mean levels of lead in blood, bone, liver, and kidney for children of different ages. These mean blood lead levels and an estimated geometric standard deviation for blood lead levels in humans can be combined to predict the frequency distribution for population blood lead levels (15).

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The Society of Environmental Geochemistry and Health (SEGH) Task Force has developed a statistical model for estimating acceptable soil lead levels based on a desired mean and range of blood-lead levels. This model utilizes statistical relationships (developed from epidemiological analyses) to describe the contribution of soil sources and non-soil sources to blood lead. Unlike the IU/BK model, the SEGH model does not require the use of assumptions for soil-dust transfer coefficients, soil ingestion rates, and lead bioavailability. Instead, the SEGH model utilizes site-specific environmental health data, such as individual-specific soil lead and blood lead levels, to determine the slope relationship between soil lead and blood lead in the population being studied (18). Once the slope relationship has been established, the frequency distribution of blood lead levels associated with given soil-lead levels can be determined.

References

- (1) ACGIH, 1986. <u>Documentation of the Threshold Limit Values and Biological Exposure Indices</u>. Fifth Edition. Cincinnati, OH: American Conference of Governmental Industrial Hygienists. ISBN-0-36712-68-6.
- (2) U.S. EPA (Office of Health and Environmental Assessment). December 1989. Integrated Risk Information System (IRIS). Washington, DC EPA/600/8-86-/032b.
- (3) U.S. EPA (Office of Emergency and Remedial Response). October 1986. <u>Superfund Public Health Evaluation Manual</u>. EPA 540/1-86/060.
- (4) ACGIH, 1988-87. Threshold Limit Values and Biological Exposure Indices for 1987-1988. Cincinnati, OH: American Conference of Governmental Industrial Hygienists. ISBN: 0936712-72-4.
- (5) Clement Associates, September 27, 1985. <u>Chemical, Physical and Biological Properties of Compound Present at Hazardous Waste Sites</u>. Final Report for U.S. EPA.
- (6) U.S. EPA (Environmental Criteria and Assessment Office). 1984. Health Effects Assessment for Lead. Cincinnati, OH. Final Report.
- (7) U.S. EPA (Environmental Criteria and Assessment Office). 1980. Ambient Water Quality Criteria for Lead. Cincinnati, OH. NTIS PB 81-117681.
- (8) Doull, J., C.D. Klaassen, M.O. Amdur; 1980. <u>Casarett and Doull's Toxicology: The Basic Science of Poisons</u>. Second Edition. Macmillan Publishing Co., Inc. ISBN 0-02-330040-X.
- (9) Agency for Toxic Substances and Disease Registry (ATSDR). July 1988. The Nature and Extent of Lead Poisoning in Children in the United States: A Report to Congress. U.S. Department of Health and Human Services.
- (10) Agency for Toxic Substances and Disease Registry (ATSDR). February 1988.

 <u>Toxicological Profile for Lead</u>. U.S. Public Health Service: Atlanta, GA. Draft for Public Comments.
- (11) Centers for Disease Control (CDC). January, 1985. <u>Preventing Lead Poisoning in Your Children</u>. U.S. Public Health Service, Atlanta, Georgia.
- (12) Sherlock, J., G. Smart, G.I. Forbes, M.R. Moore, W.J. Patterson, W.N. Richards, and T.S. Wilson. 1982. "Assessment of Lead Intakes and Dose-response for a Population in Ayr Exposed to a Plumbsolvent Water Supply." <u>Human Toxicol</u>. 1: 115-122.

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- (13) Cools, A., J.A. Salle, M.M. Verberk, and R.L. Zielhuis. 1976. "Biochemical Response of Male Volunteers Ingesting Inorganic Lead for 49 Days." Int. Arch. Occup. and Environ. Health. 38: 129-139.
- (14) Harley, N.H., and T.H. Kneip. 1985. "An Integrated Metabolic Model for Lead in Humans of All Ages." Final Report to the U.S. EPA, Contract No. B44899 with New York University School of Medicine, Dept. of Environmental Medicine, January 30, 1985.
- (15) U.S. EPA (Office Of Research & Development). March 1990. <u>Technical Support Documentaion Lead.</u> Cincinnati, OH. EPA ECAO-CIN-757.
- (16) U.S. EPA (Office of Air Quality Planning and Standards). March 1990. Review of The National Ambient Air quality Standards for Lead: Assessment of Scientific and Technical Information. Research Triangle Park, NC.
- (17) Steele, M.J. August 1990. Personal communication Gradient Offices. Cambridge MA.
- (18) Gradient Corporation. August 15, 1990. Evaluation of Two Methods to Determine Cleanup Levels for Lead in Soil. Cambridge MA.
- (19) Selevan, S.G., P.J. Landrigan, F.B. Stern and J.H. Jones. 1985. "Mortality of Lead Smelter Workers." Am. J. Epidemiol. 122: 673-683

Lead in Bone: Implications for Toxicology during Pregnancy and Lactation

by E. K. Silbergeld*

Advances in understanding the distribution and retention of lead in mineralized tissues are important for two reasons: first, bone lead may be a more accurate dosimeter of integrated absorption associated with chronic exposures, and second, bone lead may be a source of internal exposure to the host organism. Little attention has been paid to this second aspect, the remobilization of lead from bone. Mobilization of lead from bone is likely to occur during periods of altered mineral metabolism; since calciotropic factors determine the uptake and storage of lead in this compartment, changes in calcium-related regulatory factors are likely to affect lead compartmentation. Calcium metabolism changes drastically in humans during pregnancy and lactation; although relatively little is known of lead kinetics during these critical periods, it is likely that bone lead is mobilized and transferred to the more bioavailable compartment of the maternal circulation, with potential toxic effects on the fetus and the mother.

Introduction

The title of this conference, "Lead in Bone, Implications for Dosimetry and Toxicology," examines two opportunities presented by the ability to measure lead in bone. The first opportunity is the improvement in evaluating lead dose, particularly chronic, integrated dose, or the influx of lead into bone. The second opportunity is the ability to study lead in bone as a source of internal lead exposure, or the efflux of lead from bone. Understanding the effects of lead on reproduction will be advanced by using bone lead measurements for both influx and efflux of lead into this compartment.

The effects of lead on fetal growth, intrauterine development, and postnatal status have long been of concern in occupational and environmental medicine. More recently, several large epidemiological studies have reported deficits in early infant development observed in children born to mothers whose blood lead levels during pregnancy were only slightly elevated as compared to a control group (1-3). Because these exposures, as measured by blood lead, fall within the range found in much of the population of the United States, the findings have implications for defining perinatal lead toxicity as an epidemic (4). Further definition of dose response and understanding of critical time periods during pre- and postnatal development for the neurotoxic effects of lead are critical for designing appropriate screening and intervention. The data currently available do not clearly separate the effects of prenatal exposure from those of postnatal exposure, particularly in terms of relative persistence.

The two large-scale prospective studies on lead exposure in the U.S. (1,2) and the prospective study underway in Yugoslavia (5), may provide data that will help to define these issues. At present, the results from the Cincinnati study (2) have been interpreted to support a hypothesis that prenatal lead exposure results in more persistent deficits in behavior than does early postnatal exposure, while the Boston study (1) results appear to support the opposite hypothesis.

A complication in interpreting these studies lies in major uncertainties concerning lead toxicokinetics during pregnancy. The most commonly used marker for lead exposure is the measurement of lead in blood, which is a useful indicator of relatively recent or steady-state lead exposure given that the half-life of lead in this compartment is only 35 days (6). The interpretation of these studies is based on the assumption that blood lead levels usually measured once, at delivery, accurately reflect exposure of the mother and the fetus over pregnancy. However, blood levels change over pregnancy, and lead is rapidly transferred across the placenta to the fetus (7).

To evaluate fully the significance of fetal lead exposure, it is critical to know the determinants of fetal lead dose. Total fetal dose reflects not only the transfer of lead derived from mother to fetus associated with the mother's exposures during her pregnancy but also the transfer of lead stored in the mother accumulated over her prior history of lead exposure.

In addition, the mobilization of lead from bone during pregnancy and lactation may have toxic effects

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ipon the mother. Lead toxicity must reflect the pharnacodynamic interactions of lead with its intracellular sites of toxic action; the more frequently and intensively atoms of lead pass by these receptors, the more likely cell and organ level toxicity will be produced. From the perspective of the receptor, a recycled atom of lead is the same as a newly absorbed atom. Mobilization of bone lead into the circulation increases the amount of lead in the proximately bioavailable compartment of the plasma.

This paper will discuss evidence for the hypothesis that mobilization of maternal lead stores occurs during pregnancy and that this mobilization is an important factor in overall fetal exposure and potential toxic effects to both mother and fetus. Although the focus of this paper is on maternal-fetal lead toxicokinetics and toxicity, it is not meant to imply that these are the only effects of significance related to lead and perinatal development. Male-mediated exposures and effects of lead on male reproduction are not considered in this paper, but may well be of importance in assessing the overall significance of relatively low-level lead exposures on reproduction and child development.

The paper will review available data on lead kinetics during pregnancy and lactation from both clinical and experimental studies and the few case studies of effects observed in mothers and children. It will also review what is known of mineral metabolism during pregnancy since the factors regulating mineral metabolism hat respond to the physiological and hormonal changes during these periods also affect lead storage and bioavailability.

Lead Toxicokinetics during Pregnancy and Lactation

Human Data

Our information on the toxicokinetics of lead during pregnancy is indirect. As noted by Miller (8), kinetic studies in pregnancy must account for complex interrelationships involving three compartments: the mother, the fetus, and the placenta. For studies involving postnatal exposure via lactation, the child and the additional compartment of breastmilk must be included. In clinical studies, these three compartments are not readily available at the same time for sampling and analysis. Unfortunately, in most experimental studies, these compartments have not been studied in an integrated manner.

For lead, within humans, both mother and fetus, there are several compartments of kinetic importance: blood, soft tissue, and bone (9). As discussed by Rabinowitz (6), each of these compartments may have several binding and storage sites with internal fluxes that regulate overall intercompartmental fluxes and eventually maternal-fetal lead kinetics.

Two types of studies of maternal blood lead levels have been conducted during pregnancy; cross-sectional and longitudinal. The cross-sectional studies of women

at different stages of pregnancy show a tendency for decreased blood lead from the first to second trimester and relatively little change thereafter (10.11). However, these cross-sectional studies may be confounded by age, which is a significant factor in determining blood lead levels and which may influence mineral metabolism (see below). The longitudinal studies, following cohorts over pregnancy, have not shown clear trends (12,13). Studies of blood lead at delivery, based upon sampling fetal blood from the umbilical cord, indicate that lead is readily transferred across the placenta. The correlations between maternal blood lead levels and those in cord blood are almost 1.0 (5).

Lead absorption and retention by the fetus has been extensively studied by Barltrop (12). He found significant increases in lead content (but not concentration) in fetal bone and organs over gestation. A more recent study concluded that lead did not accumulate in human fetuses during the first trimester (14), which is not inconsistent with what is known of mineral metabolism over pregnancy (see below).

Two case studies provide evidence that there can be significant mobilization of lead from bone during pregnancy. One case study suggests that the mobilization of lead during pregnancy can result in relatively high-dose exposure with overt toxicological consequences for the infant (15). Over the course of pregnancy, one woman's blood lead levels increased dramatically to 74 μ g/dL, with clinical signs of intoxication and her baby's blood lead level was 55 μ g/dL. There was no evidence of increased exposure to external lead sources over this period of time. The authors determined that she had had excessive lead exposure as a young child, over 30 years prior to this pregnancy.

In another case study, Manton measured his wife's blood lead and speciated it by stable isotopic ratio. He reported changes in stable isotopic ratios that indicated contributions to blood lead over pregnancy from a pool that did not correspond to the external source of lead at the time of measurement (16).

We have investigated changes in bone lead stores somewhat more directly by using the NHANES II dataset (17). In a group of postmenopausal women, we found significant increases in blood lead concentrations as compared to premenopausal women, after controlling for age, calcium intake, and other variables potentially related to both external lead exposure and mineral metabolism (Table 1). Of relevance to this topic, we also found that in postmenopausal women who had ever been pregnant, the extent of the postmenopausal increase in blood lead was significantly less than that in nulliparous postmenopausal women (Fig. 1). These data suggest that during prior pregnancies (and possible lactation), there was some mobilization of bone lead such that less was subsequently available for mobilization during demineralization after menopause. Alternatively, nulliparous women may be more at risk for postmenopausal bone demineralization, although epidemiological studies of postmenopausal osteoporosis have not clearly shown this (18).

Table 1. Variables entered in univariate and multivariate analyses.

Lead-related variables Age (in years) Age squared Race* Income Degree of urbanization Lead used in gasoline (10° g/day) Number of cigarettes per day Alcohol drinker (greater than one drink/week) Variables related to osteoporosis Dietary calcium (mg/day) Hypertensive medication Eody mass index Subscapular skinfold (cm) Dietary phosphorus (g/day) Dietary protein (g/day) Tricep skinfeld (cm) Recreational exercise Hypothesis variables Menopause status Years since menopause Fregnancy history

* 1 - black, otherwise 0.

b 1 = less than \$5000/year; 2 = \$5000-15,000/year;

3 - \$15,000/year.

1 - cities over 3,000,000 to 8 - rural under 2500.

d Weight/height.

*1 = little or none; 2 = moderate; 3 = heavy.

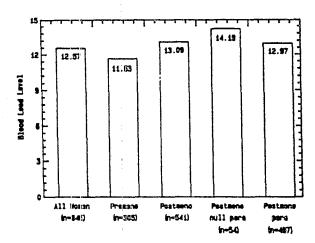


FIGURE 1. Blood lead concentrations in black and white women, aged 40 to 60 years (n = numbers in sample used for analysis). Premeno, premenopausal women; postmeno, postmenopausal women; postmeno null para, postmenopausal women with no prior pregnancies; postmeno para, postmenopausal women with at least one pregnancy. Data from NHANES II survey; see Silbergeld et al. (17) for details of analyses.

Lead is also secreted in breastmilk in a range from 0.24 to 35 mcg/dL. External exposures influence breastmilk lead levels, as expected, such that urban populations in general have higher levels than rural populations (19). Lead is found in concentrations

higher than those found in plasma at the same time (20). Breastmilk lead concentrations may increase over lactation, although no comprehensive studies have been done. Women older than 30 years had significantly higher levels of breastmilk lead than women between 20 and 30 years of age (11). This may reflect the general increase in stored and circulating levels of lead as a function of age or altered mineral metabolism during lactation in older women.

Experimental Data

Only a few studies of experimental animals exposed to lead have examined lead kinetics over pregnancy. These studies are further limited in interpretation because of incomplete design and because rodents may not be adequate models for the physiology of pregnancy in humans. These studies have confirmed that lead is rapidly transferred from mother to fetus, particularly during the late stages of gestation. Moreover, after midgestation in the rodent, the flux of lead from maternal to fetal circulation favors the placental and fetal compartments (21). Total fetal lead content of the fetus increased with time but concentration tends to decrease [as noted by Barltrop in humans (12)] because of the relatively greater rate of fetal growth during this period.

Two experimental studies have examined the potential for redistribution of lead from the mother to the fetus and infant during pregnancy and lactation. Buchet et al. (22) found that in rats exposed to lead for 150 days, whose exposure was then discontinued for 50 days prior to mating there was a substantial mobilization of lead from mother to fetus. This transfer was more pronounced in the di-continuous exposure group than in groups in which lead exposure was continued up to or through gestation, which the authors interpreted to reflect differences in bone resorption rather than lead dosage.

Keller and Doherty (23) examined lead kinetics with radiotracer lead (210Pb) in female rats over gestation and lactation. They found that the major period of bone lead mobilization occurred during lactation rather than gestation. This involved both the lead administered to lactating mothers and the mobilization of lead stored in maternal bone from prior exposure. This latter source of lead transfer from maternal bone paralleled the measured decrease in bone mineral content over the same period. However, not all this lead was transferred to the sucking infant via milk; maternal excretion of lead was also increased during lactation.

Because of the relative lack of clinical data and unavailability of information from primate models of lead toxicokinetics during these periods, interpretation of these results must be guarded. It is appropriate to conclude that there is evidence that lead metabolism changes during pregnancy and lactation and that the transfer of lead to the fetus and neonate is likely to be enhanced.

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EARLY PREGNANCY

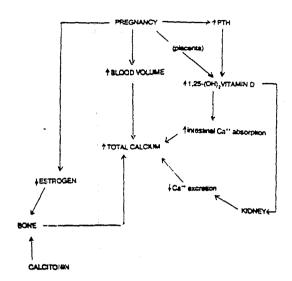


FIGURE 2. Calcium metabolism in early pregnancy. A major physiological change influencing calcium metabolism is the increase in maternal blood volume during this period; as a consequence, in order to maintain circulating levels of calcium, total calcium in the blood compartment is increased primarily through increasing intestinal calcium absorption and reducing renal calcium excretion. It is also possible that the decreased production of estrogen in pregnancy affects bone cell status through estrogen receptors in a manner similar to that observed in postmenopausal osteoporosis, that is, to increase bone resorption. The major hormonal nignals governing these changes are parathyroid hormone and 1,25-dihydroxyvitamin D, both of which are increased in the circulation.

Mineral Metabolism during Pregnancy and Lactation

Pregnancy and lactation place significant demands on the availability of calcium from the diet and from physiological stores in mineralized tissue (24,25). As shown in Figures 2 and 3, during pregnancy, two major changes affect calcium physiology: first, blood volume significantly increases, which requires increased circulating calcium to maintain normal [Ca2+], and second, the fetus exerts a demand for calcium for ossification and growth. This second requirement for calcium is greatest during the third trimester when the fetus obtains about 20 g of the total intrauterine requirement of 30 g of calcium (25,26). During lactation, an additional and even greater demand is placed upon maternal sources of calcium for the secretion of this essential mineral in breast milk (Fig. 4). These demands of the developing organism and mother have only two possible sources of supply: increased dietary sources through a change in diet and enhanced retention of exogenously derived calcium, or a draw upon calcium in bone through the modification of bone turnover to favor resorption. During pregnancy, however, along with increased calcium absorption (about twice normal levels), calcium excretion is also increased (24).)

LATE PREGNANCY

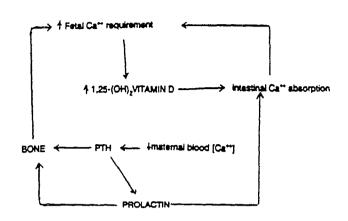


FIGURE 3. Calcium metabolism in late pregnancy (third trimester).

During this period, fetal ossification becomes a driving factor in altering maternal calcium metabolism. Calcium is supplied to the fetus, and maternal calcium metabolism is regulated by vitamin D, parathyroid hormone, and projectin.

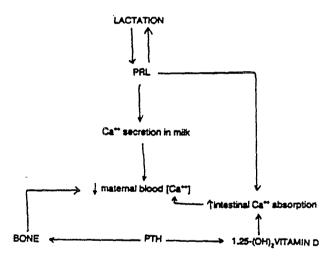


FIGURE 4. Calcium metabolism during lactation. During this period, the stress on maternal calcium metabolism is qualitatively greatest, and the extent of bone demineralization is potentially the largest. Prolactin, parathyroid hormone, and vitamin D all regulate changes in calcium metabolism during lactation.

Calcium requirements for pregnant and lactating women are much greater than those for adult men. During the last trimester, the fetus retains about 250 mg of calcium per day, generating a maternal daily intake requirement of about 1100 mg/day. During lactation, about 400 and 1600 mg/day is secreted in breastmilk each day (24). The recommended daily intake of calcium is even greater, about 1300 mg/day (25). At this time, both calcium absorption increases and calcium is drawn from bone stores.

However, there is still some controversy over calcium

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requirements during pregnancy. It has been assumed that adequate dietary intake of calcium will prevent demineralization of maternal bong (25).) However, the clinical data are still incomplete, in that many studies were not controlled for calcium intake or measurement of calcium balance. Physiologically, maternal metabolism adapts during pregnancy to exploit both external and internal sources of calcium. Dietary calcium is conserved by increasing gut absorption of calcium and decreasing renal excretion. Hormonal changes are the major factors controlling these adaptations. There is a steady and significant increase in circulating levels of 1,25-dihydroxyvitamin D during pregnancy in humans (27,28) and circulating levels of parathyroid hormone may also be increased (24). Prolactin is another major hormonal mechanism for modifying calcium metabolism during pregnancy and lactation, increasing calcium absorption and placental transfer of calcium (29,30). However, in many pregnant and lactating women, bone may be an additional source of calcium as evidenced by changes in bone formation rate, loss of bone mineral, and frank osteoporosis in some cases (31,32). Some studies have found as much as 10% loss of bone mineral in lactating women whose diets were only somewhat calcium deficient (about 900 mg/day) (33). In rats with adequate colcium and vitamin D intake, between 15 and 40% of bone mineral can be lost during lactation (34).

More detailed studies have demonstrated the complexity of bone physiology during pregnancy (Figs. 2 and 3). Purdie et al. (35) reported increased rates of resorption in early pregnancy, followed by increased rates of formation in late pregnancy, a finding paralleled by experimental studies in rats (34). This biphasic change in bone mineral status, which may result in part from changes in circulating estrogen levels could reflect a storage mechanism to provide calcium for the greater demands of lactation (Fig. 4). There is also some suggestion that different parts of bone are differentially mobilized during different phases of bone resorption, which may be of importance in estimating relative availability of lead stored in specific regions or types of bone (36).

Important Factors in Bone Lead Mobilization

It seems reasonable to conclude that bone lead is a potential source of lead for the fetus and neonate and that the kinetics of lead in bone follow those of calcium in bone during the periods of pregnancy and lactation. If this is the case, it is important to determine those factors modulating the movement of lead from bone in human pregnancy. Some of these factors are discussed below.

Lead Exposure. Integrated, cumulative lead exposure is obviously important in determining fetal and neonatal exposure from both stored lead and concurrent external exposures (7). Also, the dose rate of lead exposure may influence the location and concentration

of lead in bone and its later availability for mobilization, as suggested by Rabinowitz (6).

Maternal Age. In addition to determining body lead burden and concentrations in bone, maternal age may influence mineral metabolism. Adolescent mothers with inadequate calcium metabolism have relatively high bone loss during lactation (33). Given the prevalence of dietary deficiencies in this population and the increasing rate of pregnancy among adolescents, particularly in groups at high risk for environmental lead exposure (37), the coincidence of these two highly correlated factors, age and nutrition, may be very important for lead exposure. In another age-related observation, older women appear to secrete higher levels of lead in breastmilk than do younger women, but this may reflect general trends in lead exposure and body lead burden.

Gestational Age. Gestational age clearly influences mineral metabolism in both mother and fetus. The fetus produces 1,25-dihydroxyvitamin D and hence regulates its own active calcium uptake across the placenta (26,38). The most active phase of calcium transfer to the fetus occurs in the last trimester of pregnancy, a period that coincides with the critical phases of neurodevelopment in which synaptogenesis and arborization of the cortex and cerebellum occur (39). This coincidence is unfortunate because of the effects of lead to inhibit synaptic formation (40) and to block neurotransmitter-directed cytoarchitectural development of the brain (41).

Maternal Nutritional Status. As noted above, maternal nutrition is a major determinant of maternal mineral metabolism during pregnancy and lactation. Calcium- and vitamin D-deficient diets during these periods result in substantial bone demineralization (33). Maternal nutritional status will also affect the absorption and retention of lead; although it is not clear that supplementing the diet with calcium can reduce lead absorption or affect lead kinetics, deficiencies clearly enhance the absorption of lead (42).

Parity. Little is known of the influence of number of pregnancies upon maternal mineral metabolism. In epidemiological studies, parity number is confounded by age and weight, variables that also affect mineral physiology (43). We found that parity influenced the magnitude of postmenopausal increases in blood lead levels (17), as discussed above, but we could not examine the impact of number of pregnancies due to small sample size available for analysis of this variable. Parity is a complex variable in studies of postmenopausal osteoporosis, and number of pregnancies as well as age at pregnancy are important, although incompletely understood, factors (18).

Race. For demographic and socioeconomic reasons primarily, race is a determinant of lead exposure in American populations (37). Nutritional status also varies with race in the U.S., and calcium-deficient diets are more common among poor, disadvantaged minority women than among other groups. Race is also a variable in mineral metabolism, with black women ex-

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riencing much lower incidence of postmenopausal steoporosis than white women (18). We found a significant difference between white and black women in the relative increase in blood lead levels following menopause, consistent with a decreased loss of bone mineral in black women. Among Asian and Turkish women, osteomalacia has been diagnosed during and after pregnancy of sufficient severity to increase the risks of fractures during pregnancy and rickets in their infants (44). This condition may be due to inadequate intake of vitamin D in these populations and hence to socioeconomic and cultural factors rather than genetics.

Summary and Research Needs

This conference has focused on bone lead primarily as an improved dosimeter for determining cumulative lead exposure in specific groups at risk, primarily children and workers. However, given the lability of bone mineral stores, there are additional toxicological concerns about the potential for release of lead from bone stores during normal physiological conditions that increase bone mineral loss. Of major importance for public health is the potential mobilization of lead from bone during pregnancy and lactation, with potential toxic consequences for both the mother and the neonate.

Most attention has been paid to the potential expoure of the fetus; however, the remobilization of lead rring pregnancy and lactation may have toxic consequences for the mother as well, as lead is returned to the bioavailable compartment (plasma) and may be redistributed to such target organs as brain, heart, and kidney.

The available data are sparse. Some experimental data confirm that both dietary and stored lead are transferred to the fetus avidly and that maternal bone stores of lead may be mobilized, particularly during lactation. In humans, there is at least one case of maternal intoxication during pregnancy due to mobilization of significant bone lead stores (15). Indirect evidence for such mobilization was also found in a large population-based survey of the U.S. population, in which postmenopausal women were found to have significant increases in blood lead, but this increase was diminished by prior pregnancy (17).

If bone lead stores are a potential source of lead for the fetus, there are several important implications for the medical management of lead exposure and intervention as well as needed areas for research. First, the possible contribution of prior lead exposure, resulting in increased bone lead, must be evaluated in epidemiological studies associating lead dose with outcome in infants and young children. Second, the prior history of lead exposure may be important to determine in evaluating individuals and populations at risk. Third, "terminants of bone status during pregnancy may be

portant not only for preventing osteomalacia, hypocalcinemia, hyperphosphatemia, and other mineralrelated problems of pregnancy and the fetus, but also to prevent untoward mobilization of lead from bone. Fourth, methods for determining the overall toxico-kinetics of lead during pregnancy, particularly the flux of lead from bone to the fetus, must be developed.

There is a consensus as to the research needed in order to develop feasible implementation of bone lead measurements for better estimation of lead dose—the influx term (36). For the purpose of estimating potential exposure to bone lead—the efflux term—somewhat different research strategies may be important. For dosimetry, a stable compartment that reflects accumulation of lead over time is important; for mobilization, it is important to be able to measure lead in unstable compartments of mineral tissue and to be able to estimate rates of bone formation/absorption at the same time.

The field of lead toxicology may be transformed by the availability of new technology for measuring lead stores in bone, the major pool for lead in the body. Bone lead may prove to be a vast improvement in dosimetry and, as such, advance our understanding of the doseresponse relationships of lead at low dose and the long-term consequences of low level lead exposure. That there are children with very high bone lead stores suggests that they may be persons at considerable risk of lead toxicity whose risk is not adequately assessed by measurements of blood lead levels or chelatable lead in urine (45).

In certain populations at risk for bone demineralization for reasons of normal physiological change, aging, or disease, it may be important to determine bone lead stores as a determinant of potential risk of toxicity from mobilized lead during these periods. However, it is clear that much needs to be known about mineral metabolism and bone physiology during such periods as pregnancy and lactation in order to evaluate the potential risk of lead stored in bone for such persons.

In addition, the possibility that lead may affect the endocrinological signals regulating mineral metabolism and bone cell function requires further investigation, as suggested by Pounds (46). It may be that bone cells containing lead respond differently to the hormonal signals accompanying pregnancy, lactation, and menopause, which appear to be the determinants of altered bone status. We have suggested that lead may enhance processes of demineralization by inhibiting activation of vitamin D, decreasing calcium ab-Sorption, and interfering with hormonal signals, such as prolactin (17). Finally, these studies may at last focus attention upon bone as a target for lead toxicity. It has been remarkable that this compartment, in which the overwhelming majority of lead is stored, has long been considered as an inert depot into which lead is transferred and in which no biological response to this very toxic element was thought to occur. Advances in mineralized tissue physiology, not least the finding that most hormones that regulate bone cell status are shared by, among other organs, the brain (47), should serve to direct research toward understanding the endocrinological effects of lead and the cellular conseuences of lead in bone for bone itself and for the control of mineral flux that is regulated by bone. It has been proposed that lead-calcium interactions are the fundamental molecular mode of lead toxicity (41,48), yet little attention has been paid to that physiological system with the highest concentrations of calcium and lead and its interactions with such major functions as growth, development, reproduction, and senescence.

REFERENCES

- 1. Bellinger, D., Leviton, A., Waterneaux, C., Needleman, H. L., and Rabinowitz, M. Longitudinal analyses of prenatal and post-natal lead exposure and early cognitive development. N. Engl. J. Med. 316: 1037–1043 (1987).
- Dietrich, K., Succop, P. A., Bornschein, R. L., Hammond, P. B., and Kraffl, K. Lead exposure and neurobehavioral development in later infancy. Environ. Health Perspect. 89: 13-19 (1990).
- 3. Vimpani,
- -4. Agency for Toxic Substances and Disease Registry. The Nature and Extent of Lead Poisoning in Children in the United States. ASTDR, Repartment of Health and Human Services, Washington, DC, 1988.
- Graziano, J. H., Popovac, D., Factor-Litvak, P., Shrout, P., Kline, J. E., Murphy, M. J., Zhao, Y-H., Mehmeti, A., Ahmedi, X., Rajovic, B., Zuicer, Z., Nenezic, D. U., Lolacono, N. J., and Stein,
- Z. Determinants of elevated blood lead during pregnancy in a population surrounding a lead smelter in Kosoud, Yugoslavia. Environ. Health Parspect. 89: 95-100 (1990).
- 6. Rabinovitz, M. B. Toxicokinetics of bone lead, Environ. Health
 Perspect. 91: 33-37 (1990).
- 7. Silbergeld, E. K. Maternally mediated exposure of the fetus: in utero exposure to lead and other toxins. Neurotoxicology 7:557-2) 568 (1986).
- 8. Miller, R. K. Perinatal toxicology: its recognition and fundamentals. Am. J. Ind. Mod. 4: 205-244 (1983).
 - Marcus, A. H. Multicompartment kinetic models for lead. Environ. Res. 36: 441–489 (1985).
- 10. Alexander, F. W., and Delves, H. T. Blood lead levels during pregnancy. Int. Arch. Occup. Environ. Health 48: 35–39 (1981).
- 11. Bonithon Kopp, C., Huel, G., Grasmick, C., Sarmini, H., and Moreau, T. Effects of pregnancy on the inter-individual variations in blood levels of lead, cadmium and mercury. Biol. Res. Preg. 7: 37-42 (1986).
- 12. Barltrop, D. Transfer of lead to the human fetus. In: Mineral Metabolism in Pediatrics (D. Barltrop and L. Barland Eds.), Davis, Fhiladelphia, 1969, pp. 135-151.
- 13. Gershanik, J. J., Brooks, G. G., and Little, J. A. Blood lead levels in pregnant women and their offspring. Am. J. Obstet. Gynecol. 119: 508-511 (1974).
- 14. Borella, P., Picco, P., and Masellis, G. Lead content in abortion material from urban women in early pregnancy. Int. Arch. Occup. Environ. Health 57: 93-99 (1986).
- 15. Thompson, G. N., Robertson, E. F., and Fitzgerald, S. Lead mobilization during pregnancy. Med. J. Aust. 143: 131 (1985).
- Manton, W. I. Total contribution of airborne lead to blood lead. Br. J. Ind. Med. 42: 168-172 (1985).
- 17. Silbergeld, E. K., Schwartz, J., and Mahaffey, K. Lead and osteoporosis: mobilization of lead from bone in postmenopausal women. Environ. Res. 47: 79-94 (1988).
- Cummings, S. R., Kelsey, J. L., Nevitt, M. C., and O'Dowd, K. J. Epidemiology of osteoporosis and osteoprorotic fractures. Epidemiol. Rev. 7: 178-208 (1985).
- Ong, W. N. C., Phoon, O. W., Law, Y. H., et al. Concentrations of lead in maternal blood, cord blood, and breast milk. Arch. Dis. Child. 60: 756-759 (1985).
- Wolff, M. S. Occupationally derived chemicals in breast milk. Am. J. Ind. Med. 4: 259-281 (1983).
- Danielsson, B. R. G., Dencker, L., and Lindgren, A. Transplacental movement of inorganic lead in early and late gestation in the mouse. Arch. Toxicol. 54: 97-107 (1983).

- Buchet, J. P., Lauwerys, R., Roels, H., and Hubermont, G. Mobilization of lead during pregnancy in rats. Int. Arch. Occup. Environ. Health 40: 33-36 (1977).
- Keller, C. A., and Doherty, R. A. Bone lead mobilization in lactating mice and lead transfer to suckling offspring. Toxicol. Appl. Pharmacol. 55: 220-228 (1980).
- 24. Garel, J. M. Hormonal control of calcium metabolism during the reproductive cycle in mammals. Physiol. Rev. 67: 1-66 (1987).
- 25. Robinson, C. J., Hall, J., and Beshir, S. O. Hormonal modulation of mineral metabolism in reproduction. Proc. Nutr. Soc. 42: 169-180 (1983).
- Kuoppala, T., Tuimala, R., Parviuinen, M. and Koskinen, T. Can the fetus regulate its calcium uptake? Br. J. Obstet. Gynnecol. 91: 1192-1196 (1984).
- 27. Beyers, N., Odendaal, H. J., and Hough, F. S. Vitamin D and mineral metabolism in normal pregnancy and in the normal fetus. S.A. Med. J. 70: 549-554 (1986).
- 28. Gertner, J. M., Coustan, D. R., Kliger, A. S., Mallette, L. E., Ravin, N., and Broadus, A. E. Pregnancy as state of physiological absorptive hypercalciuria. Am. J. Med. 81: 451-456 (1986).
 - Anonymous. Prolactin and calcium metabolism in pregnancy and lactation. Nutr. Rev. 40: 216-218 (1982).
 - Pahuja, D. N., and DeLuca, H. F. Stimulation of intestinal calcium transport and bone calcium mobilization by prolactin in vitamin D-deficient rata. Science 214: 1038-1039 (1981).
- 31. Gruber, J. E., Gutteridge, D. H., and Baylink, D. J. Osteoporosis associated with pregnancy and lactation: bone biopsy and skeletal features in three patients. Metab. Bone Dis. Rel. Res. 5: 159–165 (1984).
- 32. Brommage, R., and DeLuca, H. F. Regulation of bone mineral loss during lactation. Am. J. Physiol. 248: 182–187 (1985).
- 33. Chan, G. M., McMurray, M., Westover, K., Engelbert-Fenton, K., and Thomas, M. R. Effects of increased dietary calcium intake upon the calcium and bone mineral status of lactating adolescent and adult women. Am. J. Clin. Nutr. 46: 319-323 (1987).
- 34. Miller, S. C., Shupe, J. G., Redd, E. H., Miller, M. A., and Omura,

 T. H. Changes in bone mineral and bone formation rates during pregnancy and lactation in rats. Bone 7: 283-287 (1986).
 - Purdie, D. W., Aaron, J. E., and Selby, P. L. Bone histology and mineral homeostasis in human pregnancy. Br. J. Obstet. Gynaecol. 95: 849–854 (1988).
- Nordberg, G. F., Mahaffey, K. R., and Fowler, B. A. Introduction and summary. International Workshop on Lead in Bone: implications for dosimetry and toxicology. Environ. Health Perspect. 91: 3-7 (1990).
- Mahaffey, K. R., Annest, J. L., Roberts, J., and Murphy, R. S. National estimates of blood lead levels, United States 1976-1980:
 association with selected demographic and socioeconomic factors. N. Engl. J. Med. 308: 573-579 (1982).
- Kumar, R., Cohen, W. R., Silva, P., and Epstein, F. H. Elevated 1,25-dihydroxyvitamin D plasma levels in normal human pregnancy and lactation. J. Clin. Invest. 63: 342–344 (1979).
- 39. Schwartz, M. Cortical development of the primate brain: implications for lead neurotoxicity. Paper presented at the Symposium on Advances in Lead Research: Implications for Environmental Health Sciences, January 9–11, 1989, Research Triangle Park, NC.
- Averill, D., and Needleman, H. L. Neonatal lead exposure retards cortical synaptogenesis in the rat. In: Low Level Lead Exposure (H. L. Needleman, Ed.), Raven Press, New York, 1980, pp. 201–210.
- 41. Silbergeld, E. K. Neurobiological perspective on lead toxicity.
 In: Low Level Lead Toxicity (H. L. Needleman, Ed.), CRC Press,
 Boca Raton, FL, in press.
 - 42. Mahaffey, K. R.
- Byrne, J., Thomas, R., and Chan, G. M. Calcium intake and bone density of lactating women in their late childbearing years. J. Am. Diet. Assoc. 87: 883-887 (1987).
- Park, W., Paust, H., Kaufmann, H. J., and Offermann, G. Osteo-malacia of the mother—rickets of the newborn. Eur. J. Pediatr. 146: 292-293 (1987).
- 45. Rosen, J. F., Markowitz, M. E., Bijur, P. E., Jenks, S. T., Wielo-

- polski, L., Kalef-Ezra, J. A., and Slatkin, D. N. L-line x-ray fluorescence of cortical bone lead compared with the CaNa, EDTA test in lead-toxic children: public health implications. Proc. Natl. Acad. Sci. USA 86: 685–689 (1989).
- Pounds, J. G., Long, G. J., and Rosen, J. F. Cellular and molecular toxicity of lead in bone. Environ. Health Perspect. 91:17
 32 (1990).
- Sauk, J. J., and Somerman, M. J. Physiology of bone: mineral compartment proteins as candidates for environmental perturbation by lead. Environ. Health Perspect. 91: 9-16 (1990).
- 48. Pounds, J. G. Effect of lead intoxication on calcium homeostasis and calcium-mediated cell function: a review. Neurotoxicology 5: 295–332 (1984).

THE LONG-TERM EFFECTS OF EXPOSURE TO LOW DOSES OF LEAD IN CHILDHOOD

An II-Year Follow-up Report

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Abstract To determine whether the effects of low-level lead exposure persist, we reexamined 132 of 270 young adults who had initially been studied as primary school-children in 1975 through 1978. In the earlier study, neuro-behavioral functioning was found to be inversely related to dentin lead levels. As compared with those we restudied, the other 138 subjects had had somewhat higher lead levels on earlier analysis, as well as significantly lower IQ scores and poorer teachers' ratings of classroom behavior.

When the 132 subjects were reexamined in 1988, impairment in neurobehavioral function was still found to be related to the lead content of teeth shed at the ages of six and seven. The young people with dentin lead levels >20 ppm had a markedly higher risk of dropping out of high school (adjusted odds ratio, 7.4; 95 percent con-

ITHIN the past three years, the Environmental V Protection Agency and the Agency for Toxic Substances and Disease Registry have concluded in policy statements that lead at low doses is a serious threat to the central nervous systems of infants and children. 1,2 These policy statements have been based on a growing convergence of results from both epidemiologic and experimental studies of lead toxicity in the United States, Europe, and Australia.3-8 Whether the effects on the central nervous system of exposure to low doses of lead that have been observed in infants and children persist has received limited attention. Only three follow-up studies have been published to date, and the longest follow-up has been five years. 9-11 No data have yet been reported on whether early disturbances influence functional abilities in later life.

In 1979 we reported that first- and second-grade children without symptoms of plumbism, but with elevated dentin lead levels, had deficits in psychometric intelligence scores, speech and language processing, attention, and classroom performance. When they were studied in the fifth grade, the children with high dentin lead levels had lower IQ scores, needed more special academic services, and had a significantly higher rate of failure in school than other children. We have now evaluated the neuropsychological and academic performance in young adulthood of 132 of

fidence interval, 1.4 to 40.7) and of having a reading disability (odds ratio, 5.8; 95 percent confidence interval, 1.7 to 19.7) as compared with those with dentin lead levels <10 ppm. Higher lead levels in childhood were also significantly associated with lower class standing in high school, increased absenteeism, lower vocabulary and grammatical-reasoning scores, poorer hand—eye coordination, longer reaction times, and slower finger tapping. No significant associations were found with the results of 10 other tests of neurobehavioral functioning. Lead levels were inversely related to self-reports of minor delinquent activity.

We conclude that exposure to lead in childhood is associated with deficits in central nervous system functioning that persist into young adulthood. (N Engl J Med 1990; 322:83-8.)

the original sample of 270 subjects, and we report the relation of their recent performance to their exposure to lead, as measured 11 years earlier.

METHODS

Sample

The initial sample was chosen from the population of 3329 children enrolled in the first and second grades in the Chelsea and Somerville, Massachusetta, school systems between 1975 and 1978. Of this population, 7 percent provided at least one of their shed primary teeth for lead analysis. From this sample of 2335 children, 97 percent of whom were white, we identified 270 from English-speaking homes whose initial dentin lead levels were either >24 ppm or <6 ppm. These children (mean age, 7.3 years) underwent an extensive neurobehavioral examination. More teeth were subsequently collected and analyzed, and the subjects whose teeth were discordant with respect to lead level according to a priori criteria were excluded from the data analysis. Also excluded from the analysis were children who had not been discharged from the hospital after birth at the same time as their mothers, who had a noteworthy head injury, or who were reported to have had plumbism.³

In a later reanalysis, conducted in response to suggestions from the Environmental Protection Agency,¹² the tooth lead level was treated as a continuous variable. A mean dentin lead level was computed for each subject from all the teeth collected. The exclusionary factors previously used were found not to be related to outcome scores. The subjects initially excluded were therefore not excluded from this follow-up sample.

The 270 subjects tested from 1975 to 1978 constitute the base population for this report. From old research records, telephone directories, town records, and driver's-license rolls, we located 177 subjects. Of these, 132 agreed to participate, and the remaining 45 declined. The subjects were paid \$35 each and received travel expenses. Ten subjects tested in 1988 had been excluded from the analysis reported in 1979 because their parents stated at the time of testing that the children had elevated blood lead levels or had undergone chelation for lead poisoning. This group is discussed separately in this report. The mean age of the 132 subjects at the 1988 reexamination was 18.4 years; the mean length of time between the two examinations was 11.1 years. All but four subjects in the current follow-up study were white. No clinical manifestations of lead exposure were recorded in the earlier interviews for the 122 subjects who were not treated with chelating agents.

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The research protocol and informed-consent procedures were approved by the institutional review boards of the Children's Hospital of Pittsburgh and the Children's Hospital, Boston. Informed consent was given by all the subjects or their parents.

Classification of Lead Exposure

All the dentin lead levels measured from 1975 through 1977 were used to compute an arithmetic mean lead concentration for each subject. The lead burden was treated in two ways: as an interval variable in linear regressions and as a categorical variable — i.e., high (>20 ppm), medium (10 to 19.9 ppm), and low (<10 ppm) — in the logistic regressions described below. Lead levels in venous blood were measured at the time of the reexamination to estimate current exposure. This practice was discontinued after the first 48 subjects were tested, because none had a lead level exceeding 0.34 μ mol per liter (7 μ g per deciliter), well below the Centers for Disease Control's definition of undue lead exposure of 1.25 μ mol per liter (25 μ g per deciliter).

Behavioral Evaluation

The subjects were evaluated individually by a single examiner, who remained blinded to their lead-exposure status until all the data had been coded and entered into a computer data base. All assessments were carried out in a fixed order, the duration of the testing was about two hours.

Neurobehavioral Evaluation System

The subjects completed an automated assessment battery in which they used a personal computer, joystick, and response key.¹³ We selected the following items from the battery for evaluation:

Continuous-performance test.14

Symbol-digit substitution, an adaptation of the Wechsler item for computer administration.

Hand-eje toordination. Using a joystick to move the cursor, the subject traced over a large sine wave generated on the monitor screen; deviations from the line (root mean square error) were recorded.

Simple visual-reaction time. Subjects pressed the response k., when an O appeared on the screen; the interval before the stimulus was varied randomly.

Finger tapping. The subject pressed a response button as many times as possible during a 10-second period; both hands were tested.

Pattern numory. The subject was presented with a computergenerated pattern formed by a 10-by-10 array of dark and bright elements. After a brief exposure, the subject was presented with three patterns, only one of which was identical to the original pattern. The number of correct responses and the length of time to the correct choice were recorded.

Pattern comparison. The subject was presented with three computer-generated patterns on the 10-by-10 array. Two were identical, and one differed slightly from the other two. The subject was required to select the nonmatching pattern.

Scrial-digit learning. The subject was presented with a string of 10 digits, then asked to enter the string into the computer. After an error, the same stimulus was presented, and the second trial began.

Vocabulary. For each of 25 words, the subject chose the word most nearly synonymous from a list of four choices.

Grammatural reasoning. The subject was presented with a pair of letters, A and B, whose relative position varied. Then the screen cleared, and the letters were replaced by a sentence that described the order of the letters. The sentence might be active or passive, affirmative or negative, true or false (examples are "A follows B" and "B is not followed by A"). The subject had to choose the correct sentences, and the number of errors was recorded.

Switching attention. The subject was required to choose which key to press in response to three different instructions. In the "side" trials, the subject had to press the key on the same side as the stimulus. In the "direction" trials, the correct choice was the direction in which an arrow pointed. Before each trial in the third set, the subject was told whether to choose the side the arrow was on or the direction in which it pointed."

Mood scales. This test was derived from the Profile of Mood States. 15 Five scores were computed for tension, anger, depression, fatigue, and confusion.

The following tests were also used to evaluate neurobehavioral functioning:

California Verbal Learning Test

The California Verbal Learning Test¹⁶ was used to assess multiple strategies and processes involved in verbal learning and memory. Scores for immediate and delayed recall were also obtained.

Boston Naming Test

In the Boston Naming Test, 17 the subject was presented with 60 pictures in order of increasing difficulty and asked to name the objects shown.

Rey-Osterreith Complex Figure Test

The Rey-Osterreith Complex Figure Test¹⁸ was used so evaluate visual-motor and visual-spatial skills. The subject was asked to copy an abstract geometric figure and then to draw it from memory both immediately and after 30 minutes. Accuracy and organization scores were calculated.

Word-Identification Test

Form B from the Woodcock Reading Mastery Test was used to evaluate reading skill. Grade-equivalency scores were calculated from raw scores. Reading disability was defined as indicated by scores two grade levels below the score expected on the basis of the highest grade completed.

Self-Reports of Delinquency

The subjects completed a structured questionnaire from the National Youth Survey¹⁹ that included scales for minor antisocial behavior and for violent crimes.

Review of School Records

High-school records were obtained for all but two of the subjects tested. Class size and rank, the highest grade completed, and the number of days absent and tardy in the last full semester were recorded. Students who were still in the 11th grade at the time of testing were not included in analyses of the highest grade completed. Class rank was computed as 1 - (class rank/class size).

Statistical Analysis

To evaluate whether the participants in this follow-up evaluation were representative of the original cohort, subjects who were tested and not tested in 1988 were compared in terms of variables reported in 1979, including dentin lead levels, covariates not related to lead exposure, teachers' ratings of classroom behavior, and IQ scores. In addition, we carried out separate regressions of dentin lead level against IQ score as measured between 1976 and 1978 for subjects tested and not tested in 1988. We then performed a regression on both groups taken together, entering both a dummy term for participation in the current follow-up (yes or no) and a lead-level-by-participation status term.

To evaluate the relation between early exposure to lead and each of the continuously distributed outcome variables, subjects were classified according to dentin lead-level quartiles, and mean scores, adjusted for covariates, were computed. Ordinary least-squares lin-

car regression, with the mean or log-mean dentin lead level as the main effect, was used to estimate the significance of the relation. Outcomes that were significantly associated with lead exposure in these bivariate analyses were further evaluated by multiple regress in analysis. Ten covariates were included in the model. They were the mother's age at the time of the subject's birth, the mother's exacational level, the mother's 1Q, family size, socioeconomic statas a two-factor Hollingshead index), sex, age at the time of testing, birth order, alcohol use, and whether the subject and the mother lest the hospital together after the subject's birth. The lead measure (the mean or the log of the mean) that produced the bestfitted model (highest R2) is reported. Five of these covariates were employed in the first study of these subjects and shown to be influential. Five others (sex, age at testing, prolonged hospitalization as a reonate, birth order, and current alcohol use) were added to the model on the basis of prior knowledge of their effects on psychometne function. Logistic-regression analysis was used to model the association of lead level and two outcomes treated categorically (failure to graduate from high school and reading disability). In this analysis, we controlled for the covariates listed above. Two indicator variables were used to represent the three exposure groups. Odds ratios and 95 percent confidence intervals, adjusted for covariates, were computed for the high-lead-level group, with the lowlead-level group used as the reference group.

RESULTS

Selection Bias

The 132 subjects who were retested in 1988 (Table 1) were not representative of the group of 270 subjects tested in 1979. The subjects we retested tended to have slightly lower dentin lead levels, more highly educated families of higher socioeconomic status, and mothers with higher IQs and better obstetrical histories; a higher proportion of the retested subjects were girls. In addition, they had had fewer head injuries and had significantly higher IQ scores and better teachers' ratings as reported in 1979. The slope of the regression of childhood IQ on dentin lead level was steeper in the group not tested in the follow-up study, although the difference from the slope in the group we retested was not statistically significant (F = 1.82, 1,196 df; P = 0.18).

Academic and Neurobehavioral Outcome

Table 2 shows the covariate-adjusted scores of the 122 subjects who did not have clinical plumbism, according to their dentin lead concentrations. Table 3 summarizes the results of modeling the relation between early exposure to lead and outcome by multiple regression. Earlier exposure to lead was significantly associated with diminished academic success. Among children with dentin lead levels >20 ppm, as compared with those whose denuin lead levels were <10 ppm, the unadjusted odds ratio for failure to graduate from high school was 4.6 (95 percent confidence interval, 1.2 to 17.4). Adjustment for

Table 1. Comparison of Subjects Tested and Not Tested in 1988.*

| | TESTED | NOT TESTED | |
|--------------------------------------|--------------|---------------|---------|
| CHARACTERISTIC | (N = 132) | (N = 138) | P VALLE |
| Lead-level group (%) | | | |
| Low | 50 | 47.8 | _ |
| Middle | 22.7 | 16.7 | |
| High | 27.3 | 35.5 | 0.7† |
| Birth order | 2.3=1.6 | 2.8 = 1.9 | 0.016 |
| No. of live hirths | 2.8±1.5 | 3.2 ± 1.6 | 0.05 |
| Father's education (yr) | 12.2±2.6 | 11.4 = 2.6 | 0.009 |
| Mother's education (yr) | 12.0±2.2 | 11.1=2.1 | 0.0005 |
| Mother's IQ | 112±15 | 108±15 | 0.017 |
| Mother's age at subject's birth (yr) | 25.5±5.9 | 25.3±5.8 | 0.7 |
| Father's age at subject's birth (yr) | 28.3±7.8 | 28.8±7.9 | 0.6 |
| Gestation (wk) | 39.9±2.0 | 40.0±1.7 | 0.7 |
| Birth weight (g) | 3776±608 | 3712±600 | 0.40 |
| Sea (%) | | | |
| Female Male | 55.3 44.7 | 42.8 57.3 | 0.04 |
| Head injuries (%) | 3.8 | 8.7 | 0.09 |
| Teachers' ratings (1979 sum score) | 9.3±2.8 | 8.2±3.6 | 0.004 |
| Full-scale IQ (1979) | 107.5±14 | 99.5±15 | 100.0 |

^{*}Plos-minus values are means = SD.

covariates increased the odds ratio to 7.4 (95 percent confidence interval, 1.4 to 40.8). Higher dentin lead levels were also associated with lower class rank, increased absenteeism, lower scores on vocabulary and grammatical-reasoning tests, significantly slower finger-tapping speed, longer reaction times, poorer hand—eye coordination, and lower reading scores. In subjects with dentin lead levels >20 ppm, the unadjusted odds ratio for having a reading disability, defined by a score two grades below that expected for the highest grade completed, was 3.9 (95 percent confi-

Table 2. Outcomes in Young Adulthood According to Dentin Lead Concentration in Childhood.*

| OUTCOME VARIABLE | LEAD CONCENTRATION | | | | | |
|---|----------------------|----------------------|----------------|---|--|--|
| | LOWEST (<5.9 ppm) | Low (6.0–8.2 ppm) | (8.3-22.2 ppm) | нісн <u>еят</u> (>22.2 ррса . | | |
| No. of subjects | 30 | 31. | 30 | 31 | | |
| Reading score (words read correctly) | 143.8 | 142.7 | 140.2 | 135.2 | | |
| Reading grade equivalent (grade level) | 12.2 | 11.9 | 11.2 | 10.1 | | |
| Highest grade achieved (grade level) | 11.7 | 11.9 | 11.5 | 11.3 | | |
| Class standing (percentile) | 0.60 | 0.59 | 0.48 | 0 45 | | |
| Absence from school (no. of days/ semester) | 12.0 | 12.0 | 17.9 | 20.8 | | |
| Vocabulary (words correct) | 18.0 | 16.4 | 17.6 | 14.6 | | |
| Grammatical reasoning (no. incorrect) | 13.1 | 13.0 | 12.8 | 15.8 | | |
| Hand-eye coordination? | 5.1 | 5.4 | 5.5 | 6.2 | | |
| Reaction time (msec) Preferred hand Nonpreferred hand | 246.6 241.2 | 255.5 238.2 | 267,3 258,4 | 275.1 261.2 | | |
| Finger tapping (no./10 sec) | 46.6 | 47.2 | 45.9 | 43.5 | | |

[&]quot;The subjects were divided isso groups according to lead-level quartiles. The values shows are least-square mean scores, after adjustment for covariases. Subjects with cliental plumbists have been excluded.

[†]By chi-square test for all lead-level groups

f.For hand-eye occrdination, larger numbers indicate more errors.

Table 3. Regression of Outcomes in Young Adulthood on Dentin Lead Levels in Childhood.*

| COME PARIABLE | | BIVARIATE R | EGRESSION | | | MULTIPLE R | HCKE 3700P | |
|---|---------------|-----------------------|--------------|-----------------------|----------------|-----------------------|------------|---------------|
| | R? | PARAMETER ESTIMATE | SE | Practice | R ² | PARAMETER ESTIMATE | SE | PVALUE |
| Firehest grade achieved | 0.061 | -0.027 | 0.009 | 0 008 | 0.319 | -0.027 | 0.01 | 0.013 |
| Reading grade equivalent | 0.121 | -0.07 | 0.018 | 0 0001 | 0.229 | -0.072 | 0 021 | 100 0 |
| Class standate | 0 039 | -0.006 | 0.003 | 0.048 | 0.248 | -0 006 | 0 003 | 0.048 |
| Absence from school? | 0.071 | 4.8 | 1.7 | 0.006 | 0.209 | 4.73 | 8.1 | 0.01 |
| Grammatica, reasoning | 0.051 | 0.159 | 0.062 | 0.012 | 0.197 | 0.178 | 0.068 | 0.011 |
| Vocabulary | 0.108 | -0.124 | 0.032 | 0.000 | 0.324 | -0.122 | 0.033 | 0.001 |
| Finger tappuig | 0 031 | -0.104 | 0.05 | 0.05 | 0.336 | -0.133 | 0 05 | 0.01 |
| Hand-eye ctiordination | 0.043 | 0.041 | 0.018 | 0.02 | 0.195 | 0.048 | 0.019 | 0.01 |
| Reaction time? Preferred hand Nonpreferred hand | 0.025 0.03 | 11.8 11.5 | 6.66 0.05 | 0.0 6 0.056 | 0.242 0.229 | 12.9 10.3 | 6.3 5.5 | 0 042 0.06 |
| Minor antisocial behavior | 0 025 | -0.639 | 0.36 | 0 082 | 0.306 | -0.739 | 0.35 | 0.038 |

^{*}The following covariates were controlled for in the multiple regression analysis, age, sex, birth order, family size, mother's age at the subject's birth, length of the reconstal stay at the hospital, mother's education level, mother's 10, pockedonomic status, and current alcohol use.

dence interval, 1.5 to 10.5). Adjustment for covariates increased the odds ratio to 5.8 (95 percent confidence interval, 1.7 to 19.7). For most outcomes, neither the size of the lead regression coefficients nor their standard errors were substantially changed by adjustment for covariates.

Of the 10 children with clinical plumbism (who either underwent chelation or were reported to have had elevated blood lead levels), 3 of 7 (43 percent) dropped out before graduating from high school (3 others are still in school), and 5 of 10 (50 percent) have reading disabilities. When the children with plumbism were grouped with the other subjects ac-

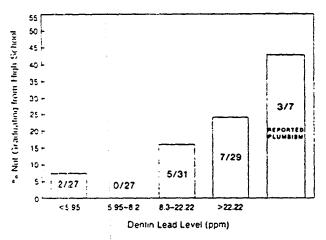


Figure 1. The Proportion of Subjects Who Did Not Graduate from High School, Classified According to Their Past Exposure to Lead.

Asymptomatic subjects are classified according to lead-level quartiles. Seven of the 10 subjects who were earlier reported to have clinical plumbism are shown in a separate column. No school records were found for two subjects. One subject was not tested but reported that she had graduated from high school. (There are therefore 121 subjects represented in this figure.) Ten subjects (three with reported plumbism and seven asymptomatic subjects) are still attending high school and are therefore not shown here. The numbers in each column indicate the number who did not graduate and the total number in the category.

cording to quartiles for dentin lead levels. a doseresponse relation was evident for both outcomes (Fig. 1 and 2).

Early exposure to lead was not significantly associated with performance on the symbol-digit or serial-digit tests, the continuous-performance test. pattern memory or pattern comparison, switching attention, the California Verbal Learning Test, the Rey-Osterreith figures, the Boston Naming Test, or mood scores. The lead level was inversely related to the summed score on the self-report of delinquency questionnaire, which consisted primarily of reports of minor antisocial behavior.

When subjects were divided into two groups according to their dentin lead levels (<10 ppm vs. ≥10 ppm), high dentin lead levels predicted future failure to graduate from high school with a sensitivity (±SE) of 0.71±0.12 and a specificity of 0.61±0.05 (Table 4).

Discussion

In this extended follow-up study, in which the mean length of follow-up was 11.1 years, we found that the associations reported earlier between lead and children's academic progress and cognitive functioning persisted into young adulthood. The persistent toxicity of lead was seen to result in significant and serious impairment of academic success, specifically a seven-fold increase in failure to graduate from high school, lower class standing, greater absenteeism, impairment of reading skills sufficiently extensive to be labeled reading disability (indicated by scores two grades below the expected scores), and deficits in vocabulary, fine motor skills, reaction time, and hand—eye coordination.

A number of issues require consideration when one is interpreting the data reported here. The first is the influence of selection bias on the associations we observed. The subjects retested in 1988 had more favorable characteristics than those who could not be located or who declined to participate. The subjects who were not retested tended to have had higher lead lev-

[&]quot;The natural log of the mean dentin lead level was used as the main effect.

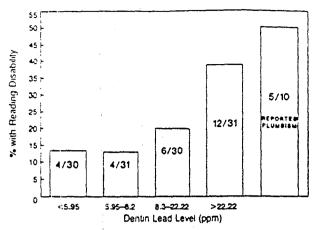


Figure 2. The Proportion of Subjects with Reading Disabilities, Classified According to Their Past Exposure to Lead.

Asymptomatic subjects are classified according to lead-level equartile, and 10 children with a history of clinical plumbism are shown separately. Reading disability is defined as indicated by a reading level two or more grades below the expected level. The numbers in each column indicate the number with a reading disability and the total number in the category.

els, lower socioeconomic status, and lower IQ scores and teachers' ratings of classroom behavior. The inverse relation between dentin lead levels and IQ reported in 1979 was stronger for the subjects who were not retested in 1988 than for those we retested, although the difference did not reach statistical significance. This finding is in agreement with the observation, made by us and others, that children from families in lower socioeconomic groups are more vulnerable to the effects of lead than children from more favored economic backgrounds.20 We infer that the estimates made on the basis of the data on the 132 subjects we restudied are likely to be conservative. Indeed, had all the original subjects been located and retested, the magnitude of the effect of lead exposure might have been even greater.

Is the nature of the relation between lead and later outcome causal, or does it result from confounding by other variables? The association between lead and outcome reported here meets six criteria for valid causal inference: proper temporal sequence, strength of association, presence of a biologic gradient, non-spuriousness, consistency, and biologic plausibility.²¹

In this study, the exposure to lead preceded the school failure and the reading disabilities measured. The strength of the association, as measured by adjusted odds ratios of 7.4 and 5.8, was substantial. A dose-response relation has been demonstrated between exposure and numerous outcome variables (Table 2, Fig. 1 and 2). "Nonspuriousness" indicates that the association observed is not due to confounding. In this analysis, we controlled for both the covariates that were identified in 1979 as potential confounders and others we suspected were important. The magnitude of the effect of lead was reduced only slightly, if at all, by this procedure. The zero-order correlation between socioeconomic status and dentin lead levels

in this sample was not great (r = 0.04). Many covariates that were important contributors to performance in the early grades (e.g., the mother's IQ and the mother's educational level) had less effect on the subject's performance in young adulthood. The results, moreover, are consistent with those of several other studies by workers who have reported leadassociated deficits in reading^{4,22,23} and early classroom behavior.24,25 The lead-related deficits in IQ, speech and language processing, and attention reported in 1979 provide plausible mechanisms by which lead could impair performance in class and produce eventual failure. Similar effects on learning have been demonstrated in the experimental studies by Gilbert and Rice of subhuman primates.7 In these investigations, rhesus monkeys, administered lead only in the first 100 days of life, had impairments in learning as adolescents. In adolescence, the mean blood lead level of these monkeys was 0.73 μ mol per liter (15 μ g per deciliter).

The value accepted as the threshold for lead-engendered neurotoxicity in children has declined steadily over the past decade as more sophisticated population studies, with larger samples, better designs, and better analyses, have been conducted. 4,5,11,22,24,26-29 When this study was begun in 1975, the toxic level of lead in the blood was defined by the Centers for Disease Control as 2.0 μ mol per liter (40 μ g per deciliter). In 1973, the mean blood lead level in a subsample of 23 children chosen from among those with the highest dentin lead levels in an earlier study was 1.7 μ mol per liter (34 μg per deciliter). None of our subjects were symptomatic. That these subjects were exposed to high doses of lead after the original study was completed is unlikely. Lead exposure, the incidence of pica, and hand-to-mouth behavior diminish after the fifth year of life. The low blood lead levels found in these subjects in young adulthood (all $< 0.034 \mu mol per liter)$ provide convincing evidence that their later exposure to lead was not excessive.

The consensus on what level of lead is toxic has changed in recent years. After reviewing the studies published up to 1987, the Agency for Toxic Substances and Disease Registry defined the threshold for neurobehavioral toxicity as 0.5 to 0.7 μ mol per liter

Table 4. Sensitivity and Specificity of the Dentin Lead Level in Childhood as a Predictor of Failure to Graduate from High School.*

| HIGH-SCHOOL GEADUATION | TEYD (EAST | | | |
|-----------------------------------|------------|---------|--|--|
| | ≥10 FFM | <10 PTM | | |
| No | 10 | 4 | | |
| Yes | 39 | 61 | | |
| Sensitivity = $10/(10+4) = 0.71$ | | | | |
| Specificity = $61/(61+39) = 0.61$ | | | | |

"Of the 122 asymptomatic subjects studied, 7 subjects who were still attending school at the time of this analysis were excluded. One subject's action records were not found. Of the 132 subjects received in 1988, the 10 with clinical planshars have been excluded.

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(10 to 15 μ g per deciliter). The agency estimated that 3 to 4 million American children have blood lead levels in excess of 0.7 μ mol per liter. The mean blood level among our subjects with high tooth lead levels, estimated in 1979 from a limited lead-screening program, was 1.6 μ mol per liter (34 μ g per deciliter) (range, 0.87 to 2.6 μ mol per liter [18 to 54 μ g per deciliter]). For subjects with low tooth lead levels, it was 1.2 μ mol per liter (24 μ g per deciliter) (range, 0.58 to 1.7 μ mol per liter [12 to 36 μ g per deciliter]). Thus, the lead levels in the reference sample used in the calculation of the odds ratios for one high-lead-level group were relatively high by contemporary standards.

The data presented here indicate that exposure to lead, even in children who remain asymptomatic, may have an important and enduring effect on the success in life of such children and that early indicators of lead burden and behavioral deficit are strong predictors of poor school outcome. For the small group of 10 subjects who were diagnosed earlier as having plumbism, the outcome was especially dire; half of these young people have reading disabilities, and almost half left high school before graduation. Given the federal estimates that 16 percent of children in the United States have elevated blood lead levels (>0.7 μ mol per liter [15 μ g per deciliter]), the implications of these findings for attempts to prevent school failure are intriguing. The practical importance of early detection and abasement of lead in the environment, before it enters the bodies of children, is borne out by these long-term findings in young adults.

We are indebted to Drs. Richard Frank, Constantine Gatsonis, Alan Mirsky, and Rolf Loeber for their careful review and critiques of the manuscript and to Ms. Pat Hadidian for her careful work in finding subjects and reviewing records.

REFERENCES

- 1 Agency for Toxic Substances and Disease Registry. The nature and extent of lead poisoning in children in the United States: a report to Congress. Atlanta: Department of Health and Human Services, 1988.
- Air quality criteria for lead. Research Triangle Park, N.C.: Environmental Projection Agency, 1986.
- Needleman HL, Gunnoe C, Leviton A, et al. Deficits in psychologic and classroom performance of children with elevated dentine lead levels. N Engl J Med 1979; 300:689-95.
- 4 Fulton M. Raab G. Thomson G. Laxen D. Hunter R. Hepburn W. Influence of blood lead on the ability and attainment of children in Edinburgh. Lances 1987: 1:1221-6.
- Hansen ON, Trillingsgard A, Beese I, Lyngbye T, Grandjean P. A neuropsychological study of children with elevated dentine lead level: assessment of the effect of lead in different socioeconomic groups. In: Lindberg SE, Hutchinson TC, eds. Heavy metals in the environment: International Conference. New Orleans. Edinburgh, Scotland: CEP Consultants, 1987:54.

- Bellinger D, Leviton A, Waternaux C, Needleman H, Rabinowitz M, Longitudinal analyses of prenatal and postnatal lead exposure and early cognitive development. N Engl J Med 1987; 316:1037-43.
- Gilbert SG, Rice DC. Low-level lifetime lead exposure produces behavioral toxicity (spatial discrimination reversal) in adult monkeys. Toxicol Appl Pharmacol 1987; 91:484-90.
- Cory-Stechta DA, Weiss B, Cox C. Delayed behavioral toxicity of lead with increasing exposure concentration. Toxicol Appl Pharmacol 1983; 71:342-57.
- Bellinger D, Needleman HL, Bromfield R, Mintz M. A follow-up study of the academic anaimment and classroom behavior of children with elevated dentine lead levels. Biol Trace Elem Res 1986; 6:207-23.
- Ernhart C, Landa B, Schell NB. Subclinical levels of lead and developmental deficit: a multivariate follow-up reassessment. Pediatrics 1981; 67: 911-9.
- Schroeder SR, Hawk B, Otto DA, Mushak P, Hicks RE. Separating the effects of lead and social factors on IQ. Environ Res 1985; 38:144-54.
- Needleman HL, Geiger SK, Frank R. Lead and IQ scores: a reanalysis. Science 1985: 227:701-4.
- Baker EL, Letz RE, Fidler AT, Shalat S, Plantamura D. A computer-based neurobehavioral and evaluation system for occupational and environmental epidemiology: methodology and validation studies. Neurobehav Toxicol Teratol 1985; 7:369-77.
- Rosvold HE, Mirsky AF, Sarason I, Bransome ED Jr, Beck LH. A continuous performance test of brain damage. J Consult Psychol 1956; 20:343-50.
- McNair DM, Lorr M, Dropleman LF. EITS manual profile of mood states. San Diego: Educational and Testing Service, 1971.
- Delis DC, Kramer JH, Kaplan E, Ober BA. The California verbal learning test — research edition. San Antonio: The Psychological Corporation, 1986.
- Kaplan E, Goodglass H, Weintraub S. Boston naming test. Philadelphia: Lea & Febiger, 1983.
- Rey A. L'examea psychologique dans les cas d'encephalopathie traumatique. Arch Psychol 1941; 28:286-340.
- Elliot DS, Huizinga AD, Ageton SS. Explaining delinquency and drug use. Beverly Hills, Calif.: Sage Publications, 1985.
- Bellinger D, Leviton A, Waternaux C, Needlemaa H, Rabinowitz M. Low level lead exposure, social class and infant development. Neurotoxicol Teratol 1988; 10:497-503.
- Hill AB. The environment and disease: association or causation? Proc R Soc Med 1965; 58:295-300.
- Fergusson DM, Fergusson JE, Horwood LJ, Kinzen NG. A longitudinal study of dentine lead levels, intelligence, school performance, and behaviour. II. Dentine lead and cognitive ability. J Child Psychol Psychiatry 1988; 29:793-809.
- Yule Q, Lansdown R, Millar IB, Urbanowicz MA. The relationship between blood lead concentrations, intelligence and attainment in a school population: a pilot study. Dev Med Child Neurol 1981; 23:567-76.
- Hatzakis A, Kokkevi A, Katsouyanni K, et al. Psychometric intelligence and attentional performance deficits in lead-exposed children. In: Lindberg SE, Hutchinson TC, eds. Heavy metals in the environment: International Conference, New Orleans. Edinburgh, Scotland: CEP Consultants, 1987;204-9.
- Yule Q, Urbanowicz MA, Lansdown R, Millar IB. Teachers' ratings of children's behaviour in relation to blood lead levels. Br J Dev Psychol 1984; 2:295-305.
- Hawk BA, Schroeder SR, Robinson G, et al. Relation of lead and social factors to IQ of low-SES children: a partial replication. Am J Ment Defic 1986; 91:178-83.
- Winneke G, Hrdina K-G, Brockhaus A. Neuropsychological studies in children with elevated tooth-lead concentrations. I. Pilot study. Int Arch Occup Environ Health 1982; 51:169-83.
- Dietrich KN, Krafft KM, Bornschein RL, et al. Low-level fetal exposure effect on neurobehavioral development in early infancy. Pediatrics 1987; 5:721-30.
- McMichael AJ, Baghurst PA, Wigg NR, Vimpani GV, Robertson EF, Roberts RJ. Port Pirie Cohort Study: environmental exposure to lead and children's abilities at the age of four years. N Engl J Med 1988; 319:468-75.

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Letter to the New England Journal of Medicine [September, 1990]

To the Editors: In their January 11 article Needleman et al. 1 report strikingly large effects of low lead levels on several late adolescence outcomes. example, an estimated 7.4-fold increased odds of school failure was attributed to childhood lead dentin levels above 20 ppm. Such massive effects sizes contrast sharply with results of other studies relating low lead level to earlier developmental outcomes 2-4. The authors argue that the estimated effects represent causal relationships because their analysis controlled for ten sociodemographic covariates. This conclusion of causality may be premature, however. because the covariate set did not include measures of the quality of child care (i.e., parental responsitivity, involvement with the child, provision of books. suitable playthings, etc.), a primary confounder in previous studies of developmental lead effects. Thus the reported lead effects may be partly due to spurious association induced by variations in the caretaking environment.

Indices of child care quality such as the HOME and the CLL have repeatedly been found to be strongly related to lead level in poor and working class children 2,4,7,4 . Quality of child care is also strongly associated with developmental outcome , including school performance through adolescence ! These confounding effects are conceptually distinct from and only partly accounted for empirically by socio-demographic variables such as maternal IQ and parental education 11, which were included as covariates by Needleman et al. The fact that none of the reported lead effects were attenuated by inclusion of their covariates, as is usually the case in observational studies of low lead levels. indicates that confounders such as child care may not have been fully controlled.

On another matter, the present report is a follow-up of a 1979 report 12 which troubled reviewers 13, in part, because many cases were excluded after testing. In a written response to the review 14 , Needleman reported data $\stackrel{\sim}{\mathcal{N}}$ indicating that a key IQ analysis was substantially affected by 16 of the \aleph excluded children with excess lead, or plumbism: Prior to exclusion, with N = 187, the lead effect \underline{t} = -1.51 (\underline{p} = .133, 2 - sided); after exclusion, with N = 171, \underline{t} = -2.56 (\underline{p} = .011). This suggests the presence of high IQ's in the plumbism group. In the present follow-up report, the previously excluded cases who agreed to participate were incorporated in the analysis, including, in separate descriptive summaries, ten of the plumbism cases. Five of these plumbism cases had reading disabilities, and three out of seven failed to graduate high school. These high proportions of adverse outcomes seem to corroborate the hypothesized lead effect. However, in view of the apparently contradictory IQ data described above, a summary of the IQ scores of all 16 plumbism cases would be helpful in assessing the implications of the findings.

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References

- 1. Needleman HL, Schell A, Bellinger D, Leviton A, Allred EN. The long term effects of exposure to low doses of lead in childhood. N Eng J Hed 1990;322: 83-8.
- 2. McMichael AJ, Baghurst PA, Wigg NR, Vimpani GV, Robertson EF, Roberts RJ. Port Pirie cohort study: Environmental exposure to lead and children's abilities at the age of four years. N Eng J Med 1988;319: 468-75.
- 3. Fergusson DM, Fergusson JE, Horwood LJ, Kinzett NG. A longitudinal study of dentine lead levels, intelligence, school performance and behaviour II. Dentine lead and cognitive ability. J Child Psychol Psychiatry 1988;29:793-809.
- 4. Ernhart CB, Morrow-Tlucak M, Wolf AW, Super D, Drotar D. Low level lead exposure in the prenatal and early preschool periods:

 Intelligence prior to school entry. Neurotoxicol Teratol 1989;11:
 161-170.
- 5. Caldwell BM, Bradley R. Home Observation for the Measurement of the Environment. Unpublished manuscript. Little Rock: Univ of Arkansas at Little Rock, 1984.
- 6. Polansky NA, Borgman RD, De Saix C. Roots of Futility. San Francisco: Jossey-Bass, 1972.
- 7. Dietrich KN, Krafft KM, Pearson DT, Harris LC, Bornschein RL, Hammond PB, Succop PA. Contribution of social and developmental factors to lead exposure during the first year of life. Pediatrics 1985;75:1114-9.

- 8. Hunt TJ, Hepner R, Seaton KW. Childhood lead poisoning and inadequate child care. Am J Dis Child 1982:136:538-542.
- 9. Bradley RH, Caldwell BM, Rock SL, Ramey CT, Barnard KE, Gray C, Hammond MA, Mitchell S, Gottfried AW, Siegel L, Johnson DL. Home environment and cognitive development in the first 3 years of life: A collaborative study involving six sites and three ethnic groups in North America. Dev Psychol 1989;25:217-35.
- 10. Hess RD, Holloway SD. Family and school as educational institutions.

 In: Parke RD, ed. The Family. Chicago: Univ. Chicago Press, 1984.
- 11. Schroeder SR, Hawk B. Psycho-social factors, lead exposure and IQ. In: SR Schroeder (Ed.) Toxic Substances and Mental Retardation:

 Neurobehavioral Toxicology and Teratology. Washington, D.C.: AAMD

 Monograph Series, 1987
- 12. Needleman HL, Gunnoe C, Leviton A, Reed R, Peresie H, Maher C, Barrett P. (1979). Deficits in psychological and classroom performance in children with elevated dentine lead levels. N Eng J Med 1979;300: 689-95.
- 13. US Environmental Protection Agency. Independent peer review of selected studies concerning neurobehavioral effect of lead exposures in nominally asymptomatic children: Official report of findings and recommendations of an interdisciplinary expert review committee.

 (EPA-600/8-83-028A).
- 14. Needleman HL. Appendix to the ECAO critique. Unpublished manuscript, on file with the Environmental Protection Agency, 1984.

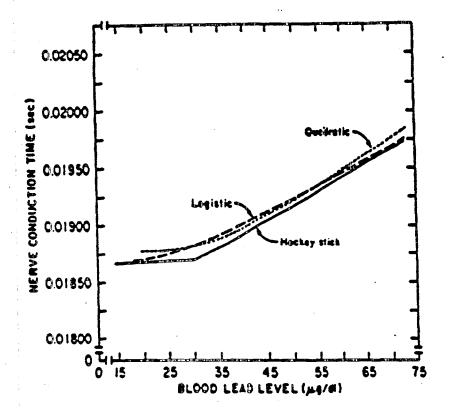


FIGURE 2-4

Haximal Nerve Conduction Time as a Function of Blood Lead Level in Children, 5-9 Years Old. Data from 202 children are fit to logistic, quadratic and "Hockey Stick" models

Source: Schwartz et al., 1988



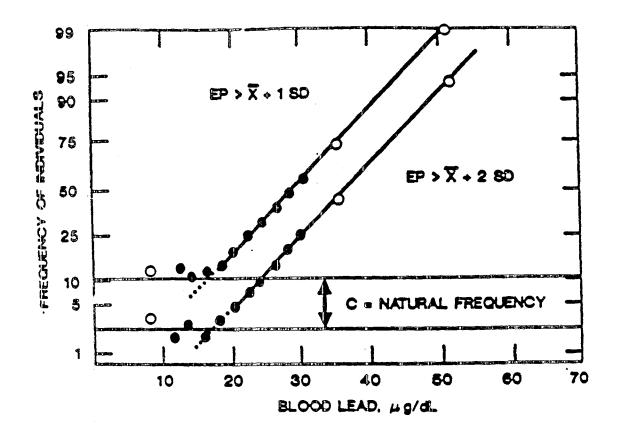


FIGURE 2-7

Probit Dose-Response Functions for Elevated Erythrocyte Protoporphyrin as Function of Blood Lead Level in Children. Geometric Mean + 1 SD = 33 μ g/dL; Geometric Mean + 2 SD = 53 μ g/dL

Source: Piomelli et al., 1982



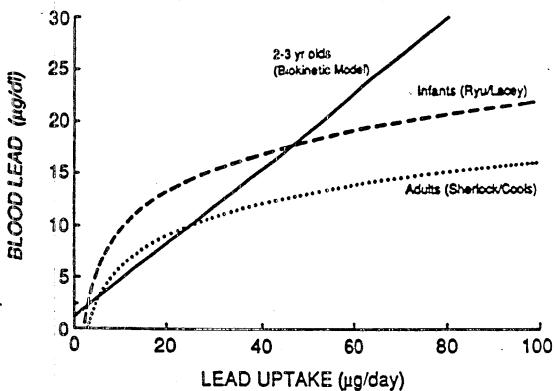
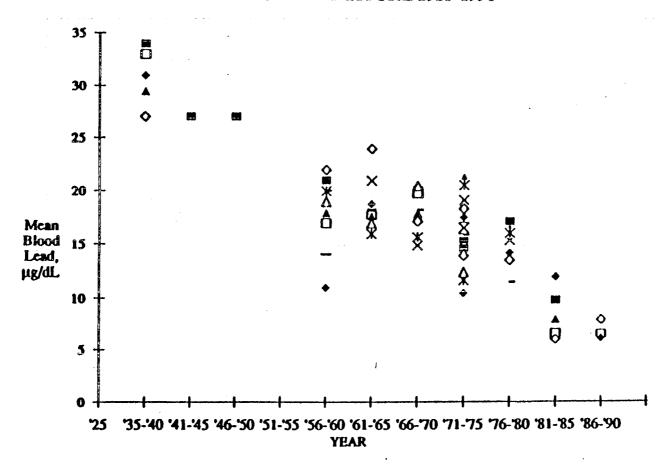


FIGURE 4-4

Summary of Relationships Between Daily Lead Uptake and Blood Lead for Infants (Ryu et al., 1983; Lacey et al., 1983), Adults (Sherlock et al., 1982; Cools et al., 1976) and 2- to 3-Year-Old Children, Derived From the lead for et al.. 2025546286286 Harley and Kneip (1985) Blokinetic Model

Source: U.S. EPA, 1989a

FIGURE 1 - U.S. BLOOD-LEAD VALUES FROM LITERATURE 1935-1990



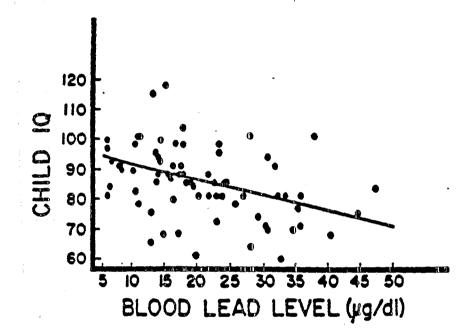


FIGURE 2-2
Child IQ as a function of Blood Lead Level in Children 3-7 Years Old
Source: Schroeder and Hawk, 1987

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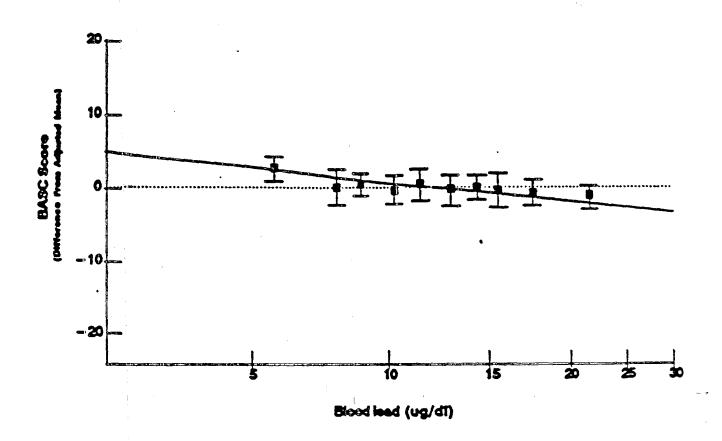
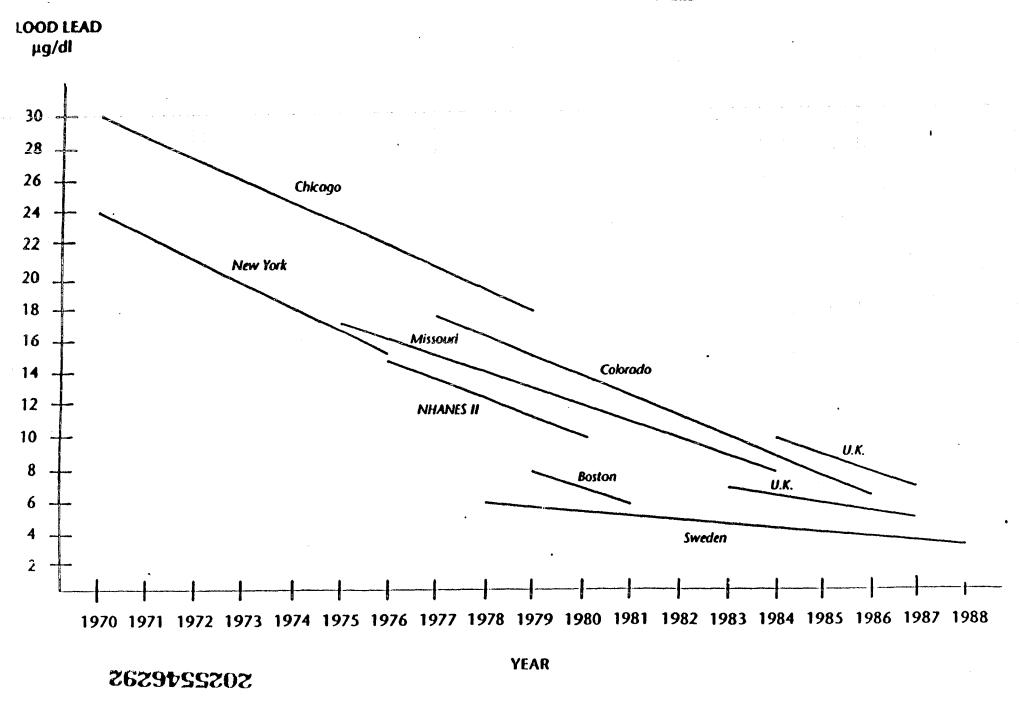


FIGURE 2-3

British Ability Scales Combined Score (BASC, Means and 95% Confidence Intervals) as a Function of Blood Lead Level in Children 6-9 Years Old

Source: Fulton et al., 1987

FIGURE 2 - TIME TRENDS IN BLOOD LEAD LEVELS



| | Α | 8 | С | D | E | F | G | Н | |
|-----|-------|------|---------|-------|-------|----------|---------------------------|-----------|---------|
| 1 | | | Mea | | | | | | |
| 2 | | | Blood l | Lead, | | | • | | - [|
| 3 | Point | | μg/100 |) ml | No. i | n | | | 1 |
| 4 | No. | Year | or /10 | 0 g | Grou | p | Location | Referen | ice |
| 5 | | | | | | <u> </u> | | | - |
| 6 | 1 | 1935 | 58 | | 71 | | U.S.A. | Kehoe | 1 |
| 7 | 2 | 1936 | 34 | | 89 | | St. Louis | McMillen | 2 |
| 8 | 3 | 1938 | 33 | | 36 | | Phila., PA | Smith | 3 |
| 9 | 4 | 1938 | 31, | | 126 | | Baltimore | Kaplan | 4 |
| 10 | 5 | 1939 | 27 | | 30 | | U.S.A. | Kehoe | 5 |
| 11 | 6 | 1939 | 29.5 | | 22 | | Phila., PA | Letonoff | 6 |
| 12 | 7 | 1946 | 27 | | 30 | | U.S.A. | Kehoe | 7 |
| 13 | 8 | 1956 | 28.5 | | 261 | | Cincinnati | 3-City | 8 |
| 14 | 9 | 1960 | 21 | | 81 | | L.A., CA | 3-City | 8 |
| 15 | 10 | 1960 | 17 | | 93 | | L.A., CA | 3-City | 8 |
| 16 | 11 | 1960 | ii | | 37 | į | Alpine Co., CA | 3-City | 8 |
| 17 | 12 | 1960 | 22 | | 123 | | New Orleans | Hofreuter | 9 |
| 18 | 13 | 1960 | 18 | | 128 | | i)allas | Hofreuter | 9 |
| 19 | 14 | 1960 | 19 | | 131 | | Denver | Hofreuter | 9 |
| 20 | 15 | 1960 | 20 | | 97 | | Chicago | Hofreuter | 9 |
| 21 | 16 | 1960 | 20 | | 112 | | New York | Hofreuter | 9 |
| 22 | 17 | 1960 | 20 | | 137 | | Cincinnati | Hofreuter | 9 |
| 23 | 18 | 1960 | 14 | | 162 | | Rural Ohio | Hofreuter | 9 |
| 24 | 19 | 1961 | 18 | | 237 | | Phila., PA | 3-City | 8 |
| 25 | 20 | 1962 | 17.7 | | 518 | | L.A., CA | 3-City | 8 |
| 26 | 21 | 1962 | 18.8 | | 10 | | Washington, DC | Siegel | 10 |
| 27 | 22 | 1963 | 24 | | 381 | | Cincinnati | 3-City | 8 |
| 28 | 23 | 1963 | 17.7 | | 47 | | Pasadena | Butt | 11 |
| 29 | 24 | 1963 | 17 | | 33 | | California | Goldwater | 12 |
| 30 | 25 | 1963 | 21 | | 105 | | New York | Goldwater | 12 |
| 31 | 26 | 1963 | 16 | | 40 | | Ohio | Goldwater | 12 |
| 3 2 | 27 | 1967 | 20.1 | | 490 | | U.S.A. | McLaughl | lin 1 3 |
| 33 | 28 | 1968 | 19.8 | | 528 | | U.S.A. | McLaughl | lin 13 |
| 3 4 | 29 | 1969 | 17.5 | | 193 | | Pasadena | Tepper | 1 4 |
| 35 | 30 | 1969 | 17.2 | | 80 | | Los Alamos | Tepper | 1 4 |
| 36 | 31 | 1969 | 18 | | 150 | | Ardmore | Террег | 14 |
| 37 | 32 | 1969 | 20.5 | | 136 | | Rittenhouse Sq., Phil. PA | Tepper | 1 4 |
| 38 | 33 | 1969 | 14.9 | | 191 | | Los Alamos | Tepper | 1.4 |
| 39 | 34 | 1969 | 15.7 | | 162 | | Okeana, OH | Tepper | 14 |
| 40 | 35 | 1970 | 18.3 | | 869 | | U.S.A. | McLaugh | lin 13 |
| 41 | 36 | 1971 | 15.3 | | 198 | | Port Washington, NY | Tepper | 14 |
| 42 | 37 | 1971 | 16.6 | | 140 | | Greenwich Village, NY | Tepper | 1 4 |
| 43 | 38 | 1971 | 17.6 | | 147 | | Bridgeport, IL | Tepper | 14 |
| 44 | 39 | 1971 | 13.9 | | 208 | | Lombard, IL | Tepper | 14 |

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| | A | 8 | <u> </u> | D E | F | G | H | |
|-----|-----|------|----------|----------|--------------|-----------------|------------|-----|
| 45 | 40 | 1971 | 12.5 | 191 | | Houston | Tepper | 14 |
| 4 5 | 41 | 1971 | 19.2 | 219 | | Washington, DC | Tepper | 14 |
| 47 | 42 | 1972 | 19.2 | 420 | | U.S.A. | McLaughlin | 15 |
| 4 8 | 43 | 1973 | 11.7 | 403 | | S. California | Goldsmith | 16 |
| 4 9 | 44 | 1973 | 15.9 | 114 | | Hartford | Osborne | 17 |
| 50 | 45 | 1973 | 17 | 76 | | Honolulu | Joselow | 18 |
| 51 | 46 | 1974 | 14.6 | 89 | ı | Ann Arbor, MI | Hecker | 19 |
| 5 2 | 47 | 1974 | 16.4 | 126 | ! | Los Angeles | Johnson | 20 |
| 53 | 48 | 1974 | 10.5 | 119 | 1 | Lancaster, CA | Johnson | 20 |
| 54 | 419 | 1975 | 18.4 | 36 | | Houston | Johnson | 21 |
| 5 5 | 50 | 1975 | 21.3 | 36 | i | Houston | Johnson | 21 |
| 56 | 51 | 1975 | 12.4 | 81 | | Houston | Johnson | 21 |
| 57 | 52 | 1975 | 16.6 | 258 | | U.S.A. | Baker | 22 |
| 58 | 53 | 1975 | 20.6 | 236 | · ' | Fontana, CA | Wei Liang | 23 |
| 59 | 54 | 1976 | 17.2 | 56 | | Upstate, NY | Perkins | 24 |
| 60 | 55 | 1976 | 15.7 | 60 |) | Salt Lake City | Smith | 25 |
| 61 | 56 | 1977 | 14.2 | 76 | | Culver City, CA | Report | 26 |
| 62 | 57 | 1977 | 13.5 | 25 | i | Culver City, CA | Report | 26 |
| 63 | 58 | 1977 | 16.3 | 19 |) | U.S.A. | Hammond | 27 |
| 64 | 59 | 1978 | 16.3 | 67 | | Culver City, CA | Report | 26 |
| 6 5 | 60 | 1978 | 15.4 | 43 | | Culver City, CA | Report | 26 |
| 66 | 61 | 1978 | 16.1 | 44 | | Culver City, CA | Report | 26 |
| 67 | 62 | 1979 | 11.5 | 9 | | Atlanta | Landrigan | 28 |
| 68 | 63 | 1981 | 9.85 | 695 | | Louisville | Angell | 29 |
| 69 | 64 | 1982 | | 6* 11837 | | Poston, MA | Rabinowitz | - 1 |
| 70 | 65 | 1983 | 12 | 122 | | Pinehurst, ID | CDC | 31 |
| 71 | 66 | 1983 | 6 | 61 | | Helena, MT | CDC | 31 |
| 72 | 67 | 1983 | 8 | | | Festus, MO | Phillips | 32 |
| 73 | 68 | 1986 | | 5* 216 | | Boston, MA | Bellinger | 33 |
| 74 | 69 | 1986 | 6.5 | 118 | | Cleveland, OH | Emhart | 34 |
| 7.5 | 70 | 1986 | 6.1 | 258 | | Telluride, CO | Albert | 35 |
| 76 | 71 | 1987 | 8 | 305 | 5 | Cincinnati, OH | Dietrich | 36 |
| 77 | | | | | | | | 1 |
| 78 | | | • | | | | | |

U.S. BLOOD LEAD LITERATURE DATA 1935 - 1990

- (1) Kehoe, R. A., Thamann, F. and Cholak, J., "Normal Absorption and Excretion of Lead Journal of the American Medical Ass'n, 104, pp. 90-92, 1935.
- (2) McMillen, J. H. and Scott, G. H., "Spectrographic Studies of Lead in Human Blood," Proceedings of the Society for Experimental Biology and Medicine, 35, pp. 364-365, Dec. 1936.
- (3) Smith, F. L. 2nd, Rathmell, T. K. and Marcil, G. E., "The Early Diagnosis of Acute and Latent Plumbism," American Journal of Clinical Pathology, 8, pp. 471-508, 1938.
- (4) Kaplan, E. and McDonald, J. M., "Blood Lead Determinations as a Health Department Laboratory Service," <u>American J. of Public Health</u>, 32, pp. 481-486, May 1942.
- (5) Kehoe, R. A., Cholak, J. and Story, R. V., "A Spectrochemical Study of the Normal Ranges of Concentration of Certain Trace Metals in Biological Materials," <u>The Journal of Nutrition</u>, 19, pp. 579-592, 1940.
- (6) Letonoff, T. V. and Reinhold, J. G., "Colorimetric Determination of Lead Chromate by Diphenylcarbazide. Application of a New Method to Analys's of Lead in Blood, Tissues, and Excreta," Ind. and Eng. Chem., Analytical Edition, 12, pp. 280-284, May 15, 1940.
- (7) Kehoe, R. A., Conference on Lead Poisoning, Seventh Annual Congress on Industrial Health, Boston, pp. 36-54, September 30 October 2, 1946.
- (8) "Survey of Lead in the Atmosphere of Three Urban communities," U.S. Public Health Service Publication, No. 999-AP-12, Environmental Health Series, Air Pollution, Jan. 1965.
- (9) Hofreuter, D. H., Catcott, E. J., Keenan, R. G. and Xintaras, C., "The Public Health Significance of Atmospheric Lead," Arch. Env. Health. 3, pp. 568-574, 1961.
- (10) Siegel, G. S., "Lead Exposure Among Decorative and House Painters," Arch. Env. Health, 6, pp. 720-723, 1963.
- (11) Butt, E. M., Nusbaum, R. E., Gilmour, T. C., DiDio, S. L., and Sister Mariano, "Trace Metal Levels in Human Serum and Blood," <u>Arch. Env. Health</u>, 8, pp. 52-57, Jan. 1964.
- (12) Goldwater, L. J. and Hoover, W. A., "An International Study of Normal' Levels of Lead in Blood and Urine," Arch. Env. Health. 15, pp. 60-63, July 1967.
- (13) McLaughlin, M., et al., "Longitudinal Studies of Lead Levels in a U.S. Population," Arch. Env. Health, 27, pp. 305-311, Nov. 1973.
- (14) Tepper, L. B. and Levin, L. S., "A Survey of Air and Population Lead Levels in Selected American Communities," Department of Environmental Health, Kettering Laboratory, University of Cincinnati, Final Report, 1972.

- (15) McLaughlin, M. and Stopps, G. J., "Smoking and Lead," presented at American Academy of Occupational Medicine, Pittsburgh, Feb. 1972.
- (16) Goldsmith, J. R., "Food Chain and Health Implications of Airborne Lead," Epidemiological Studies Laboratory, California State Department of Health, September 1974.
- Osborne, R. G., et al., "The Influence of Environmental Factors on Maternal and Neonatal Blood Lead Levels," Connecticut Medicine, 40, No. 7, pp. 452-455, July 1976.
- (18) Joselow, M. M., et al., "Environmental Contrasts: Blood Lead Levels of Children in Honolulu and Newark," J. Env. Health, 37, No. 1, pp. 10-12, 1974.
- (19) Hecker, L. E., et al., "Heavy Metals in Acculturated and Unacculturated Populations," Arch. Env. Health. 29, pp. 181-185, October 1974.
- (20) Johnson, D. E., et al., "Levels of Platinum, Palladium, and Lead in Populations of Southern California," Env. Health Perspectives, 12, pp. 27-33, 1975.
- (21) Johnson, D. E., et al., "Trace Metals in Occupationally and Non-Occupationally Exposed Workers," Env. Health Perspectives, 10, pp. 151-158, April 1975.
- (22) Baker, E. L., et al., "A Nationwide Survey of Heavy Metal Absorption in Children Living Near Primary Cu, Pb and Zn Smelters," Ameridan Journal of Epidemiology, 106, No. 4, pp. 261-273, 1977.
- (23) Wei Liang, et al., "Study on Hazards of Leaded Gasoline," Clinical Pediatrics, pp. 791-794, September 1977.
- (24) Perkins, K. C., et al. "Elevated Blood Lead in a 6-Month-Old Breast-Fed Infant: The Role of Newsprint Logs," Pediatrics, 57, No. 3, pp. 426-427, March 1976.
- (25) Smith, T. J., et al., "Cadmium, Lead and Copper Blood Levels in Normal Children," Clinical Toxicology, 9 (1), pp. 75-87, 1976.
- (26) "Report on Study of Blood Lead Concentration in Culver City School Children," Table 1 (no formally published reference).
- (27) Hammond, P. B., et al., "Relationship of Biological Indices of Lead Exposure to the Health Status of Workers in a Secondary Lead Smelter," <u>Journal of Occupational Medicine</u>, 22, No. 7, July 1980.
- (28) Landrigan, P. J., et al., "Lead Exposure in Stained Glass Workers," American Journal of Industrial Medicine, 1, pp. 177-189, 1980.
- (29) Angell, N. F., et al., "The Relationship of Blood Lead Levels to Obstetric Outcome," American Journal of Obstetrics and Gynecology, 142 (1), pp. 40-46, 1982.
- (30) Rabinowitz, M. B., Needleman, H. L. (1982) "Temporal trends in the lead concentrations of umbilical cord blood," Science (Washington, DC), 216, pp. 1429-1431.

- (31) CDC [Centers for Disease Control] (1983), Kellogg Idaho Child Lead Study, Summer 1983. Panhandle District Health Department, Idaho Dept. of Health and Welfare; U.S. EPA. July 1986.
- (32) CDC [Centers for Disease Control] East Helena, Montana Child Lead Study, Summer 1983. Lewis and Clark county Health Dept., Montana Dept. of Health and Environ. Sci., U.S. Dept. of Health and Human Services, U.S. EPA. July 1986.
- (33) Phillips, P. E., Vornberg, D. L. (1986) "Pediatric blood lead levels in Herculaneum, Missouri-1984," Presented to the Society for Environmental Geochemistry and Health at the 20th Annual Conference on Trace Substances in Environmental Health, Columbia, MO, June 5, 1986.
- (34) Bellinger, D., Leviton, A., Rabinowitz, M. Needleman, H., Waternaux, C. (1986), "Correlates of low-level lead exposure in urban children at 2 years of age," <u>Pediatrics</u>, 77, pp. 826-833.
- (35) Ernhart, C. B., Wolf, A. Q., Kennaro, M. J., Erhard, P., Filipovich, H. F., Sokol, R. J. (1985), "Intrauterine exposure to low levels of lead: the status of the neonate," <u>Arch. Environ. Health</u>, 41, pp. 287-291.
- (37) Albert, R. A., Bornschein, R. L., Clark, C.S., "Telluride, Colorado, Child Lead Survey, Fall, 1986, Institute of Environmental Health, University of Cincinnati."
- (36) Dietrich, K. M., Kraff, K. M., Bornschein, R. L., Hammond, P. B., Berger, O., Succop, P. A., Bier, M. (1987), "Low-level fetal lead exposure effect on neurobehavioral development in early infancy," <u>Pediatrics</u>, 80, pp. 721-730.

REVIEW

1989 Alice Hamilton Lecture¹

Lead and Human Health: Background and Recent Findings

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This paper, prepared in tribute to Dr. Alice Hamilton on her 120th birthday, reviews her pioneering studies of occupational lead poisoning and its control, her largely unheeded warnings about the possible consequences of widespread lead exposure to the general public through the use of leaded fuel, and the results of recent studies of human exposure to and health effects of lead in the general environment. Evidence is presented for dose-related non-threshold effects for children with blood lead concentrations below 25 µg/dl for a variety of effects including verbal IQ; mental development; physical size; and age at physical milestones such as first steps, hearing thresholds, and postural sway. For adults, various studies have produced associations between blood pressure and blood lead concentrations below 35 µg/dl, suggesting possible effects on cardiovascular health. While the biological mechanisms responsible for these effects remain poorly understood, recent and current efforts to reduce exposure to lead by the virtual elimination of lead in gasoline and food packaging show that we have learned one of Dr. Hamilton's important lessons, i.e., that the most effective means of reducing excessive exposures are through control of the environmental sources. e 1990 Academic Press, Inc.

INTRODUCTION

The invitation to present the second Alice Hamilton lecture led me to reread her autobiography (Hamilton, 1943) Exploring the Dangerous Trades (Fig. 1) which, in turn, led me to select lead's effects on human health as the focus of this lecture. The systematic study of lead poisoning among industrial workers which Dr. Hamilton performed so well, virtually single-handedly, in Illinois in 1910 led her, and those she influenced, to new careers in occupational medicine and worker health protection. Her emphasis on exposure prevention through the application of engineering controls to process technology gave powerful impetus to the development of the field of industrial hygiene in this country.

Dr. Hamilton was personally persuasive. She had to be. As she has written:

Our procedure in the Illinois survey and in the work that I carried on later for the Federal government was completely informal. We had no authority to enter any plant, we had no instructions as to which we should visit, we simply explored the state. When we found a place which seemed to belong in our field, we asked permission to enter it. Never were we refused, never did I, at least, meet with anything but courtesy in those very early days.

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EXPLORING THE DANGEROUS TRADES

The Autobiography
of
ALICE HAMILTON, M.D.



Wak Illustration by North Hamilton
AN ATLANTIC MONTHLY PRINGROOM
LITTLE, BROWN AND COMPANY - BUSTON
BALL

Fig. 1. Frontispiece and title page of Exploring the Dangerous Trades.

As Dr. Hamilton noted, however, it was usually difficult to convince management that the conditions and exposures she observed were sufficient to warrant controls. As a good example she cites the following:

... the National Lead Company... had several white-lead and lead-oxide works in and near Chicago. I visited them and found much dangerous work going on in all of them. One of the vice-presidents, Edward Cornish, later president, came to Chicago and I went to see him in the Sangamon Street works. He was both indignant and incredulous when I told him I was sure men were being poisoned in those plants. He had never heard of such a thing; it could not be true; they were model plants. He went to the door and shouted to a passing workman to come in. "Did the lead ever make you sick?" he demanded. The man, a badly scared Slav stammered, "No, no, never sick." "Any other men sick?" demanded Mr. Cornish, "no, no, all good," and the poor man escaped quickly. "There", said Mr. Cornish, "you see!" "But I do not see," I answered. "Your men are breathing white-lead dust and red lead and litharge and the furnes from the oxide furnaces. They are no different from other men; a poison is a poison to them as it is to any man." He thought a moment and then he said, "Now, see here. I don't believe you are right, but I can see you do. Very well then, it is up to you to convince me. Come back here with proof that my men are being leaded and I give you my word I will follow all your directions, even to employing plant doctors."

It was not an easy task I faced, tracking down actual, proved cases of lead poisoning among men who came from the Serbian, Bulgarian, and Polish sections of West and Northwest Chicago, and were known to the employing office only as Joe, Jim, or Charlie, with no record of their street and number! It meant digging up hospital records, for I had to be sure of the diagnosis, then a search for the home, and finally an interview with the wife to discover where the man had been working, for of course no hospital interne ever noted where the victim of plumbism had acquired the lead. Hospital history sheets noted

In the end I was able to present Mr. Cornish with authentic records of twenty-two cases of plumbism severe enough to require hospital care. He was better than his word. Beginning with the Sangamon Street works, he went on to reform all the plants in the Chicago region, and this meant dust and fume prevention, often by methods which had never before been worked out. There were no models to follow: the engineers faced new problems. As each was solved, Mr. Cornish sent the blueprints to the plants in other states and later on, when I visited these, invariably I found the same changes being introduced. I had told Mr. Cornish he could never fully protect his men unless he employed doctors to keep strict watch over their condition, to make at least a brief inspection of each lead worker once a week. He accepted this recommendation without protest and before our report was published there was a medical department in each plant of the National Lead Company in Illinois. I have met many admirable men in industry throughout these thirty-two years, but my warmest gratitude and admiration goes to Edward Cornish.

In commenting on the lack of adequate governmental regulation of occupational exposures, and the apparently automatic opposition of industry to tighter regulation Dr. Hamilton remarked:

Perhaps it is our instinctive American lawlessness that prompts us to oppose all legal control, even when we are willing to do of our own accord what the law requires.

It is clear that Dr. Hamilton was a shrewd and wise observer as well as an inquisitive investigator and pioneer. It is now also clear that failure to pay close attention to her farsighted concerns about tetraethyl lead in 1925 has had serious public health consequences.

The use of organic compounds of lead as antiknock motor vehicle fuel additives has clearly been the dominant source of a worldwide dispersion of lead into the environment and into people. Since leaded gasoline was introduced in 1923, it has increased background levels everywhere, including the Greenland ice cap (Fig. 2).

Several years ago, Rosner and Markowitz (1985) reviewed the public health controversy over leaded gasoline during the early 1920s, including the role played by Dr. Hamilton. The following is a selective condensation of their review. The introduction of leaded gasoline led to a series of fatalities and severe poisonings among employees of the producing companies in Bayway, New Jersey; Dayton, Ohio; and Deepwater, Delaware. On the other hand, in February 1924 the Bureau of Mines concluded that ethyl gas posed no threat to the public on the basis of a series of toxicological studies it performed in its laboratories with funds donated by the industry. In response to the public controversy which ensued, Dr. Hamilton wrote to Surgeon General Hugh Cumming in February 1925 suggesting the "desirability of having an investigation made by a public body which will be beyond suspicion."

In April 1925, the Surgeon General announced that he was calling together experts from business, labor, and public health to assess the tetraethyl lead situation. The conference convened on May 20, 1925. According to Rosner and Markowitz, the industry position could be summed up as follows: (1) "leaded gasoline was essential to the industrial progress of America"; (2) "any innovations entails certain risks"; and (3) "the major reason that deaths and illnesses

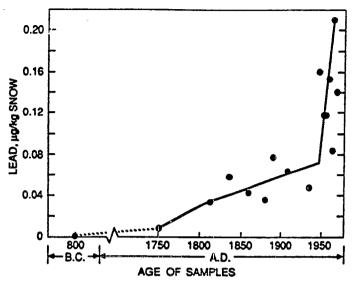


Fig. 2. Lead concentration, profile in snow strata of Northern Greenland (EPA, 1986).

occurred at their plants was that the men who worked with the materials were careless and did not follow instructions." The strongest and most authoritative critic of industry was Dr. Yandell Henderson, a noted physiologist at Yale. The following are excerpts from Rosner and Markowitz (1985).

He (Henderson) told the conference that lead was a serious public health menace that could be equated to the serious infectious diseases then affecting the nation's health. Unlike industry spokespeople who defined the problem as one of occupational health and maintained that individual vigilance on the part of workers could solve the problem, Henderson believed that leaded gasoline was a public health and environmental health issue that required federal action. He expressed horror at the thought that hundreds of thousands of pounds of lead would be deposited in the streets of every major city in America. His warning to the conference of the long-term dangers proved to be an accurate prediction: "conditions would grow worse so gradually and the development of lead poisoning will come on so insidiously... that leaded gasoline will be in nearly universal use and large numbers of cars will have been sold... before the public and the government awaken to the situation."

Dr. Hamilton agreed with those opposed to tetraethyl lead. At the conference she expressed her belief that the environmental health issues were far more important than the occupational health and safety issues, adding that she doubted that any effective measures could be implemented to protect the general public from the hazards of widespread use of leaded gasoline. "You may control conditions within a factory," she said, "but how are you going to control the whole country?" In an extended commentary after the conference on the issues that it raised, Hamilton stated, "I am not one of those who believe that the use of this leaded gasoline can ever be made safe. No lead industry has ever, even under the strictest control, lost all its dangers. Where there is lead some cases of lead poisoning sooner or later develops, even under the strictest supervision."

Most public health professionals did not agree with Henderson and Hamilton, however. Many took the position that it was unfair to ban this new gasoline additive until definitive proof existed that it was a real danger. In the face of industry arguments that oil supplies were limited and that there was an extraordinary need to conserve fuel by making com-

bustion more efficient, most public health workers believed that there should be overwhelming evidence that leaded gasoline actually harmed people before it was banned. Dr. Henry F. Vaughan, president of the American Public Health Association, said that such evidence did not exist. "Certainly in a study of the statistics in our large cities there is nothing which would warrant a health commissioner in snying that you could not sell ethyl gasoline," he pointed out. Vaughan acknowledged that there should be further tests and studies of the problem but that "so far as the present situation is concerned, as a health administrator I feel that it is entirely negative."

Despite the widespread ambivalence on the part of public health professionals and the opposition to any curbs on production on the part of industry spokespeople, the public suspicions aroused by the preceding year's events led to a significant victory for those who opposed the sale of leaded gasoline. At the end of the conference, the Ethyl Corporation announced that it was suspending the production and distribution of leaded gasoline until the scientific and public health issues involved in its manufacture could be resolved. The conference also called upon the Surgeon General to organize a blue ribbon committee of the nation's foremost public health scientists to conduct an investigation of leaded gasoline. Among those asked to participate were David Edsall of Harvard University, Julius Steiglitz of the University of Chicago, C.-E. A. Winslow of Yale University and the American Public Health Association. For Alice Hamilton and other opponents of leaded gasoline, the conference appeared to be a major victory for it wrested from industry the power to decide on the future of an important industrial poison, and placed it in the hands of university scientists. "To anyone who had followed the course of industrial medicine for as much as ten years," Alice Hamilton remarked one month after the conference, "this conference marks a great progress from the days when we used to meet the underlings of the great munition makers [during World War I] and coax and plead with them to put in the precautionary measures . . . This time it was possible to bring together in the office of the Surgeon General the foremost men in industrial medicine and public health and the men who are in real authority in industry and to have a blaze of publicity turned on their deliberations."

As a result of their study, the committee concluded seven months after the conference that "in its opinion there are at present no good grounds for prohibiting the use of ethyl gasoline... provided that its distribution and use are controlled by proper regulations." They suggested that the Surgeon General formulate specific regulations with enforcement by the states. This group saw their study as only an interim report, to be followed by longer range follow-up studies in ensuing years. In their final report to the Surgeon General, the committee warned: "it remains possible that if the use of leaded gasoline becomes wide-spread conditions may arise very different from those studied by us which would render its use more of a hazard than would appear to be the case from this investigation. Longer experience may show that even such slight storage of lead as was observed in these studies may lead eventually in susceptible individuals to recognizable or to chronic degenerative diseases of a less obvious character."

Recognizing that their short-term investigation was incapable of detecting such danger, the committee concluded that further study by the government was essential: "In view of such possibilities the committee feels that the investigation begun under their direction must not be allowed to lapse... It should be possible to follow closely the outcome of a more extended use of this fuel and to determine whether or not it may constitute a menace to the health of the general public after prolonged use or other conditions not now foreseen ... The vast increase in the number of automobiles throughout the country makes the study of all such questions a matter of real importance from the standpoint of public health and the committee urges strongly that a suitable appropriation be requested from Congress for the continuance of these investigations under the supervision of the Surgeon General of the Public Health Service."

In view of what we now know about the health effects of low levels of lead in the body, it is quite unfortunate that the further investigations called for by the

Surgeon General's committee did not take place for more than four decades, during which lead was spread far and wide in quantities which the committee could hardly have envisaged. For example, in 1970, when lead use in gasoline peaked, 252,654 metric tons were used and the total consumption over the period 1929–1983 was 6,635,059 metric tons. Of this, approximately 10% was retained in the engine oil, 15% deposited in the exhaust system, 35% emitted as submicrometer-sized aerosol, and 40% emitted as >10-\(mu\)m particles (EPA, 1986).

REVIEW OF HUMAN EXPOSURE AND HEALTH EFFECTS

Quoting once again from Dr. Hamilton's Exploring the Dangerous Trades:

Lead is the oldest of the industrial poisons except carbon monoxide, which must have begun to take its toll soon after Prometheus made the gift of fire to man. In Roman days, lead poisoning was known, for Pliny the Elder includes it among the "diseases of slaves," which were potters' and knife grinders' phthisis, lead and mercurial poisoning.

Throughout all the centuries since then men have used this valuable metal in many ways, and from time to time an observant physician has seen the results and described them, notably Ramazzini in the eighteenth century, and early in the nineteenth century the great Frenchman, Tanquerel des Planches. It is a poison which can act in many different ways, some of them so unusual and outside the experience of the ordinary physician that he fails to recognize the cause. I could never feel that I had uncovered all the cases in any community, no matter how small, even after I had talked with all the doctors and gone through the hospital records, for some doctors would not pronounce a case to be due to lead poisoning unless there was either colic or palsy, which is as if he refused to recognize alcoholism unless there were an attack of delirium tremens.

It is true that a severe attack of colic is the most characteristic symptom of lead poisoning, and palsy—usually in the form of wristdrop—is the one most easily recognized, but there are many other manifestations of this protean malady, as every physician knows today. Thirty years ago it was not hard to find extremely severe forms, such as could come only from an exposure so great as to seem criminal to us now, but which then attracted no attention.

Dr. Hamilton was writing about the situation as of 1942. By then, as now, overt clinical symptoms of lead poisoning only occurred when available knowledge about lead toxicity and exposure control are not taken into account. In 1970, 3 months after Dr. Hamilton passed away, the federal Occupational Safety and Health Act (OSHA) was passed. This led, in 1971, to the adoption of an interim Permissible Exposure Level (PEL) of 200 μ g/m³ for lead dust in air. In 1979, a permanent OSHA standard was implemented. It specified a PEL of 40 μ g/m³, as well as a blood lead concentration limit of 50 μ g/dl.

More subtle health effects, resulting from exposures below the PEL, are known to occur and were addressed by the Environmental Protection Agency (EPA) in preparing the 1978 National Ambient Air Quality Standard (NAAQS) of 1.5 µg/m³ as a 3-month average. While EPA has completed its latest criteria document for lead in ambient air (EPA, 1986), it has not yet proposed a revised NAAQS. However, concern about low-level lead exposure has led EPA to propose, on 8/18/88, a maximum contaminant level goal (MCLG) for drinking water of zero (CFR 53 (160) 31516). EPA is also considering regulating lead as a carinogen, as a toxic component in incinerator ash, and as a leachable constituent in Superfund sites.

Yaffe et al. (1983) reported that the isotopic ratios of lead in the blood of children were close to the average lead ratios of paints from exterior walls and to the lead ratios of surface soils in adjacent areas where the children played. Their data suggest that the lead in the soil was derived mainly from weathering of lead-based exterior paints, and that the lead-contaminated soil was a proximate source of lead in the blood of the children.

As shown in Fig. 3, the most significant contributors to current body burdens of lead include direct air inhalation, inhalation or direct ingestion of settled dust, and the ingestion of food and water. Some old housing stock has lead pipe which can elevate potable water concentrations substantially. Lesser, but still significant, elevations can occur in water delivered via modern copper and brass pipe due to leaching of lead from the solder in the joints. Foods can be enriched in lead from a variety of sources. Lead in the air can deposit on leafy vegetables and fruits and

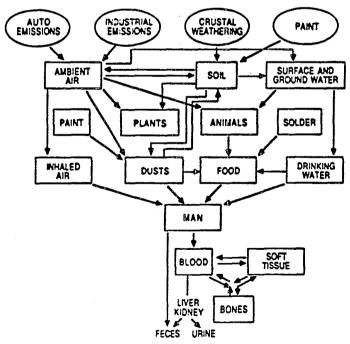


Fig. 3. Pathways of lead from the environment to and within man (EPA, 1986).

leave residues which are ingested. Lead in the soil can be incorporated into the growing plant. Canned foods can also extract lead from solder used to seal the

Lead exposures and blood lead levels among the general population have declined substantially in recent years. The most substantial reduction has been due to the switch from leaded to unleaded gasoline as motor vehicle fuel. This had an immediate effect on air lead (Fig. 4) and a parallel reduction in average blood lead (PbB) concentration which lagged by ~3 months (Fig. 5). The lag occurred because most of the tailpipe lead reached people indirectly through exposure to resuspended soil and through incorporation into foodstuffs. Further reductions have occurred as the food packaging industry has reduced the use of solder in cans. Table 1 from the 1986 EPA Criteria Document summarizes the contributions to lead in blood from the major sources for 2-year-old children in the early 1980s.

RECENT HEALTH EFFECTS FINDINGS

The literature on human exposures to lead and their health effects is voluminous. The 1986 EPA criteria document was published in four volumes containing 1336 pages. This discussion will be limited to the more descriptive research relative to low-level population exposures and the chronic health effects associated with such exposures. In most cases, this limits the review to studies of the associations between exposure and health effects in humans, since the low-dose effects of interest have seldom been seen in animal toxicology studies conducted at higher levels of exposure. The disturbing implication that conventional animal

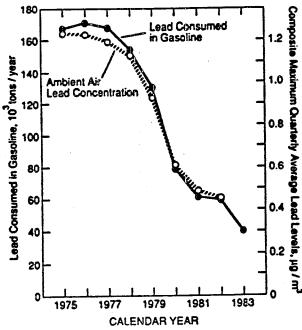


Fig. 4. Lead consumed in gasoline and ambient lead concentrations, 1975-1983 (EPA, 1986).

Fig. 5. Parallel decreases in blood lead values observed in the NHANES II Study and amounts of lead used in gasoline during 1976-1980 (EPA, 1986).

toxicology provides little useful information about some serious human chronic health issues is a subject for another paper and will not be discussed further here.

The effects that have been associated with blood lead (PbB) concentrations <40 µg/dl will be the main focus of this selective review. These include the effects of prenatal and early childhood exposures on physical and neurobehavioral development of children, and the influence of chronic low-level exposure on cardiovascular function in adults. These low-exposure-related effects are of interest in relation to both occupational and general environmental exposures. The effects in young children may be due to exposures in utero of working mothers (Wang et al., 1989), and to lead brought into the home on work clothing of family members with occupational exposures (Baker et al., 1977; Kaye et al., 1987; Wang et al., 1989).

TABLE 1

Contributions from Various Media to Blood Lead Levels (µg'dl) of U.S. Children

(Age = 2 Years): Background Levels and Incremental Contributions from Air

| | | | | Air lead, µg/m³ | ,'m³ | | |
|----------------------------|-------------|------|------|-----------------|-------|-------------|-------|
| Source | 0 | 0.25 | 0.50 | 0.75 | 1.00 | 1.25 | 1.50 |
| Background—non-air | | | | | | | |
| Food, water, and beverages | 2.37 | 2.37 | 2.37 | 2.37 | 2.37 | 2.37 | 2.37 |
| Dust | 0.30 | 0.30 | 0.30 | 0.30 | 0.30 | 0.30 | 0.30 |
| Subtotal | 2.67 | 2.67 | 2.67 | 2.67 | 2.67 | 2.67 | 2.67 |
| Background-air | | • | | | | | |
| Food, water, and beverages | 1.65 | 1.65 | 1.65 | 1.65 | 1.65 | 1.65 | 1.65 |
| Ingested dust (with Pb | | | | | | | |
| deposited from air) | 0.00 | 1.57 | 3.09 | · 4.70 | 6.27 | 7.84 | 9.40 |
| Inhaled air | 0.00 | 0.50 | 1.00 | 1.50 | 2.00 | 2.50 | 3.00 |
| Total | 4.32 | 6.39 | 8.41 | 10.52 | 12.59 | 14.66 | 16.72 |

Table 2 shows PbB levels in children of workers from a Colorado plant making capacitors and resistors (Kaye et al., 1987).

Neurobehavioral and Developmental Effects in Children

The 1986 EPA criteria document on lead contains a thorough critical review of the literature on the neurobehavioral effects of chronic lowlevel lead exposures in children. While various maladaptive behaviors, neuropsychological deficits, and neuroanatomical changes have been associated with chronic exposures to relatively low concentrations of lead, no single mechanism appears sufficient to account for the diverse effects. It is more likely that lead acts at several cellular and subcellular sites. Lead readily enters the brain and appears to be selectively deposited in the hippocampus and cortex as well as in nonneuronal elements that are important in the maintenance of "blood-brain barrier" functions. Once deposited, lead is retained in the brain for long periods of time even after external exposure ceases and PbB levels decline. These spatial and temporal patterns of brain lead accumulation correspond to neurobehavioral and morphologic abnormalities associated with lead exposure. The sensitivity of the brain during the period of maximal brain growth and differentiation in the first 2 years of life tends to magnify the severity of the long-term consequences.

Low PbB levels may contribute to behavioral disorders, such as attentional deficits and distractibility in essentially normal children not diagnosed as hyperactive. A study by Bellinger et al. (1984) suggests that measures of classroom performance may show long-term effects of early lead exposure. Silva et al. (1986) found similar results on 11-year-old children. Winneke et al. (1983) found that behavioral and attentional deficits as rated by teachers (e.g., disordered classroom activity, restless, easily distracted, not persistent, does not follow directions, low overall functioning) were significantly associated with children's tooth and PbB levels, which was consistent with the earlier association reported by Needleman et al. (1979). The 1986 EPA criteria document has interpreted the Winneke et al. (1983) study, which also assessed lead-induced deficits in IQ and other psychometric tests, as showing overall neurobehavioral deficits at PbB levels possibly below 30 µg/dl.

In addition, lead levels in young children have been consistently associated,

TABLE 2
BLOOD LEAD IN LEAD WORKERS' CHILDREN, BY AGE STRATA®

| | | | Blood lead (μg/dl) | | | | |
|---|----------------------|-----|----------------------|----------------------|--|--|--|
| | Age category (years) | | Exposed mean (range) | Unexposed mean (rang | | | |
| _ | <6 | | 13.4 (4-23) | 7.1* (1–13) | | | |
| | 6-10 | .50 | 11.1 (3-22) | 7.0 (5-9) | | | |
| | >11 | 7.9 | 8.0 (1-22) | 5.0* (2-11) | | | |
| | All ages | | 10.2 | 6.2* | | | |

^{*} Statistically significant (P < 0.001) between exposed and unexposed groups, Student's test.

Kaye et al., 1987.

following appropriate adjustments, with deficits in reaction time under varying intervals, which is an index of attentiveness, and with reaction behavior. The 1986 EPA criteria document concluded that these findings argue for probable effects of lead on attention and vigilance functions at PbB levels extending below 30 μ g/dl, and possibly, down to as low as 15–20 μ g/dl.

There is also evidence that low levels of lead may be associated with effects on some complex cognitive functions including learning, visual-perception skills, and IQ scores. The studies on children have attracted controversy because of difficulties associated with attributing subtle deficits in child development to lead exposure rather than to effects due to genetics, nutrition, medical history, access to education, and parental and social influences, all of which interact in potentially complex ways to mold an individual.

On the basis of five methodological criteria (adequate markers of lead exposure, sensitive measures of neurobehavioral function, appropriate subject selection, control of confounding covariates, and appropriate statistical analysis), the 1986 EPA criteria document identified a group of neurobehavioral studies that were conducted rigorously enough to warrant at least some consideration. The general indication from the better investigations is that PbB levels persistently elevated in the range of 50-70 µg/dl tend to be associated with about a 5-point reduction in IQ, even among asymptomatic children and after controlling for potentially confounding variables.

However, considerable uncertainty has existed regarding lead's impact on IQ scores of children with PbB levels below 40 μ g/dl. This uncertainty stems largely from the complex interaction between lead exposure over time, social factors, and intelligence scores, from the statistical and methodological limitations of cross-sectional studies to untangle these variables, and the range of interpretations that result from these studies.

The 1986 EPA criteria document concluded from the Needleman et al. (1979) study and subsequent reanalyses (Needleman, 1984) that, after controlling for confounding variables including pica, average IQ decrements of about 4 points and other neurobehavioral deficits appear to be associated with lead exposures of U.S. children resulting in dentine lead values that exceed 20-30 ppm and likely average PbB levels in the 30-50 μ g/dl range. Needleman et al. (1982) calculated that a 4-point decrement in the mean IQ of a normal population distribution would be associated with a threefold increase in the number of children with severe deficits (IQ < 80) along with a 5% reduction in the number of children who attain superior function (IQ > 125) (see Fig. 6).

In order to avoid the normal array of confounding factors, Bellinger et al. (1987) performed a longitudinal analysis of prenatal and postnatal lead exposure and early cognitive development in 249 children. In general, the infants were healthy products of unremarkable pregnancies, with few of the characteristics of infants at increased risk of developmental handicap. Eighty-seven percent of the families were white, and 92% were intact. The differences among the families with infants in the three cord-blood lead groups were slight and generally not in the direction expected on the basis of studies of the social correlates of childhood lead exposure. On the basis of lead levels in umbilical-cord blood, children were assigned

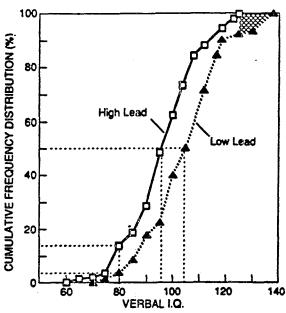


Fig. 6. Cumulative frequency distribution of verbal IQ scores in subjects with low or high levels of lead (Needleman et al., 1982).

to one of three prenatal-exposure groups: low (<3 μ g/dl), medium (6 to 7 μ g/dl), or high (>10 μ g/dl). Development was assessed semiannually, beginning at the age of 6 months, with use of the Mental Development Index of the Bayley Scales of Infant Development.

Regression methods for longitudinal data were used to evaluate the association between infants' lead levels and their development scores after adjustment for potential confounders. At all ages, infants in the high-prenatal-exposure group scored lower than infants in the other two groups. The results are summarized in Fig. 7. Scores were not related to infants' postnatal blood lead levels.

McMichael et al. (1988) studied the effect of environmental exposure to lead on children's abilities at the age of 4 years in a cohort of 537 children born during 1979 to 1982 to women living in a community situated near a lead smelter at Port Pirie in Australia. Samples for measuring blood lead levels were obtained from the mothers antenatally, at delivery from the mothers and umbilical cords, and at the ages of 6, 15, and 24 months and then annually from the children. Concurrently, the mothers were interviewed about personal, family, medical, and environmental factors. Maternal intelligence, the home environment, and the children's mental development (as evaluated with use of the McCarthy Scales of Children's Abilities) were formally assessed.

The mean blood lead concentration varied from 9.1 μ g/dl in midpregnancy to a peak of 21.2 μ g/dl at the age of 2 years. The blood lead concentration at each age, particularly at 2 and 3 years, and the integrated postnatal average concentration were inversely related to development at the age of 4. Results of multivariate

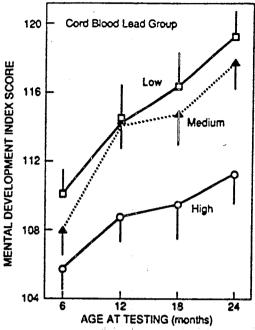


Fig. 7. Prenatal exposure to lead, as measured by umbilical cord blood lead levels vs early mental development index. Low is $\leq 3 \mu g/dl$, medium is 6.7 $\mu g/dl$, and high is $\geq 10 \mu g/dl$ (Bellinger et al., 1987).

analysis are illustrated in Fig. 8. Within the range of exposure studied, no threshold dose for an effect of lead was evident.

This cohort study indicates that a raised blood lead concentration in early childhood has an independent deleterious effect on mental development as evaluated at the age of 4 years. This effect was not accounted for by the known and measurable influences of obstetrical, parental, family, and social environmental factors on mental development. The results of this analysis and those of an earlier analysis of the children at the age of 2 years suggest that increased exposure to lead results in a developmental deficit, not just developmental delay.

Bhattacharya et al. (1988) found that abnormalities in children's abilities to maintain physical balance were significantly associated with PbB. Their postural sway on a balance increased by $\sim 2.8 \text{ cm}^2/\mu\text{g/dl}$. These data suggest that low levels of PbB affect the peripheral nervous system as well as the central nervous system. A sample of their results are illustrated in Fig. 9.

Schwartz and Otto (1987) used the large database available from the Second National Health and Nutrition Examination Survey (NHANES II), conducted between 1976 and 1980 on population samples selected as being representative of the civilian, noninstitutionalized U.S. population. For a subsample of 4519 youths ages 4-19 years, there were data available on blood Pb, audiometry, and various indicators of neurological development, such as age at which a child first sat up, walked, and spoke. The presence of speech difficulties and hyperactivity was also

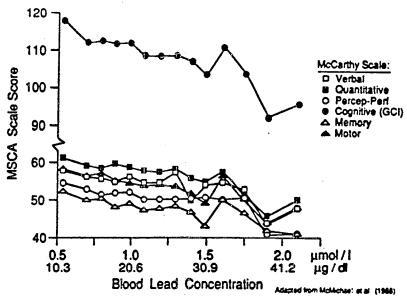


Fig. 8. McCarthy scales of children's abilities (MSCA) scores at the age of 4 vs blood lead concentration at 3 years of age (McMichael et al., 1988).

examined to determine if they were significantly related to lead exposure. The probability of elevated hearing thresholds at 500, 1000, 2000, and 4000 Hz increased significantly (P < 0.0001) with increasing PbB (Fig. 10). PbB levels were also significantly related to delays in the age at which children first sat up (Fig. 11), walked, and spoke and to the probability that a child was hyperactive. Lead was not related to the probability of a child having a previously diagnosed speech impairment.

Table 3 shows the variables considered in the stepwise multiple regressions, while Table 4 shows the levels of significance of the associations between blood lead and the developmental variables. The results of this large population study are clearly consistent with, and strongly supportive of, the validity of the associations between blood lead and neurobehavioral effects in the smaller populations reviewed earlier.

In another examination of NHANES II data, Schwartz et al. (1986) incorporated medical history, physical examination, anthropometric measurements, dietary information (24-hr recall and food frequency), laboratory tests, and radiographs in linear regressions of adjusted data from 2695 children ages 7 years and younger. They reported that 91% of the variance in height, 72% of the variance in weight, and 58% of the variance in chest circumference (Fig. 12) were explained by six variables: age, race, sex, blood lead level, total calories or protein, and hematocrit or transferrin saturation level.

In summary, there are a number of well-designed studies which indicate that very low levels of exposure to lead affect neurobehavioral function and development in young children. These various effects appear to be consistent with the

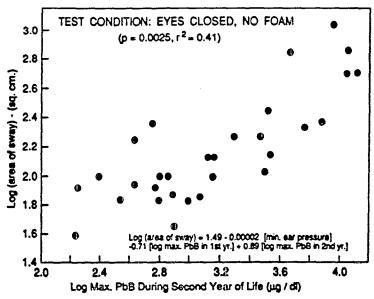


Fig. 9. National logarithm of postural sway of children at 6 years of age vs natural log blood lead concentration during second year of life after controlling for blood lead during first year of life (Bhattacharya et al., 1988).

effects of lead on heme biosynthesis which have been postulated to lead to erythropoietic, neural, renal endocrine, and hepatic effects in the body, as summarized in Fig. 13 from the 1986 EPA criteria document.

Effects of Lead in the Blood on Blood Pressure

The 1986 EPA criteria document on lead also provided a critical review of studies showing associations between blood lead concentrations less than $40 \mu g/dl$ and blood pressure. It reviewed the influence of a number of environmental and nutritional factors affecting blood pressure in experimental and epidemiological studies. Among environmental factors that have been associated with blood pressures are lead (Pb) and noise. Among dietary factors associated with blood pressure are calcium (Ca), zinc (Zn), phosphorus (P), alcohol consumption, and vitamins A and C.

The role of Pb as a pollutant stressor for elevated blood pressure could well be confounded by the well-established role of Ca as a suppressor of blood pressure. It is possible that persons with high Ca consumption have both decreased blood pressure and reduced blood Pb due to the competition of both Pb and Ca for the same binding sites. The influence of the other cofactors known to affect blood pressure further complicates the task of establishing the extent to which Pb constitutes a significant risk factor for elevated blood pressure.

A consistent pattern of results emerges from recent investigations of the relations between lower-level lead exposures and increases in blood pressure or hypertension. Khera et al. (1980) reported higher blood lead levels in hypertensive

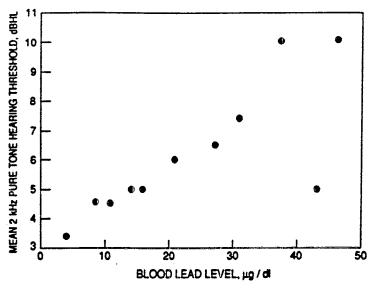


Fig. 10. Relationship of 2 kHz pure tone hearing threshold (right ear) and blood levels in 4519 NHANES II subjects ages 4-19 years. Each point represents the mean hearing threshold of all persons in a 5 µg/dl blood lead range, except for the last point, which represents the mean hearing threshold and mean blood lead for all children with blood lead levels over 35 µg/dl (Schwartz and Otto, 1987).

patients and those with other cardiovascular diseases than for hospital control subjects. Kromhout and Couland (1984) and Kromhout et al. (1985) reported associations between hypertension and blood lead among elderly men in the Netherlands. Batuman et al. (1983) reported an association between hypertension and chelatable lead burdens in veterans. Moreau et al. (1982) reported significant associations (P < 0.001) between blood lead levels and a continuous measure of blood pressure among French policemen after controlling for important potential confounding variables such as age, body mass index, smoking, and drinking. Weiss et al. (1986) reported that after correction for previous systolic blood pressure, body mass index, age, and smoking, a high level of blood lead was a significant predictor of subsequent elevation of systolic pressure in policemen in Boston. Sharp et al. (1988) examined relationships between blood lead concentration and blood pressure in San Francisco bus drivers. The analysis was limited to subjects not on treatment for hypertension (n = 288). The blood lead concentration varied from 2 to 15 µg/dl. While the findings were not statistically significant, they did suggest effects of lead exposure at lower blood lead concentrations than those previously linked with increases in blood pressure. In a follow-up study, Sharp et al. (1989) examined the relationship between blood pressure and blood lead concentration in 51 bus drivers who were treated for hypertension. These drivers were a subset of a representative sample (n = 342) of the driver population (n = -2000) and were not selected for hypertension or lead exposure. Blood lead concentrations ranged from 2 to 24 µg/dl. There were 33 subjects

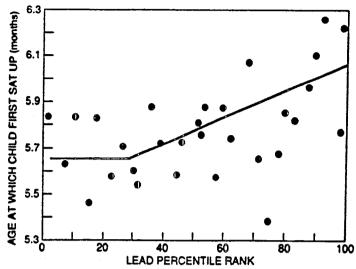


Fig. 11. Relationship of developmental milestone attainment and blood lead levels in NHANES II subjects. Plots of age at which a child first sat up (in months) vs PbB, after adjusting for other significant covariates. Each point represents the mean adjusted developmental index for 99 consecutive observations ordered by mean blood lead level. Regression lines were derived from individual data (Schwarz and Otto, 1987).

treated primarily with diuretics, and 18 subjects were treated with beta blockers. There was a significant mean difference of 12 mm Hg in diastolic BP over the range of observed Pb in blood (2.0 to 11.4 µg/dl) in subjects treated with beta blockers (see Fig. 14). Thus, beta blocker therapy may be less effective in reduc-

TABLE 3

VARIABLES USED IN STEPWISE REGRESSIONS

| A. Aud | iometric analyses | | |
|-----------------------------|-----------------------------------|--|--|
| Race | Sex | | |
| Lead | Current cold | | |
| Ear discharge | Ringing in ear(s) | | |
| Cold in last 2 weeks | Earache | | |
| Other ear condition | Previous running ear | | |
| Chronic ear discharge | Diagnosed hearing impairment | | |
| Income | Degree of urbanization | | |
| Dietary calcium | Head of household education level | | |
| B. Developme | ental milestone analyses | | |
| Race | Sex | | |
| Lead | Income | | |
| Size | Head of household education level | | |
| Dietary protein | | | |
| Total iron binding capacity | Transferrin saturation | | |
| Serum iron | Hemoglobin | | |
| Dietary calories | Weight | | |

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TABLE 4
RESULTS OF DEVELOPMENTAL MILESTONE ANALYSES

| Effect | Coefficient | P value |
|---|-------------|---------|
| A. Age (in years) at first word | | |
| Intercept | 1.25 | |
| Sex | -0.087 | 0.0277 |
| Lead rank | 0.0024 | 0.0094 |
| B. Age (in months) when first walked | | |
| Intercept | 10.88 | |
| Race | -0.655 | 0.0006 |
| Lead rank | 0.0070 | 0.0020 |
| C. Age (in months) when first sat up | | |
| Intercept | 5.68 | |
| Protein intake | -0.0039 | 0.0361 |
| Lead rank | 0.0061 | 0.0239 |
| D. Probability of being hyperactive (logistic regression) | | |
| Intercept | -4.505 | |
| Lead rank | 0.0116 | 0.0150 |

ing diastolic pressure in individuals with elevated PbB, even at PbB levels associated with exposures below the current ambient standard and far below the current occupational standard.

In a large population study, Pocock et al. (1984) evaluated the relationships between blood lead concentrations, hypertension, and renal function indicators in a clinical survey of 7735 middle-aged men from 24 British towns. The association

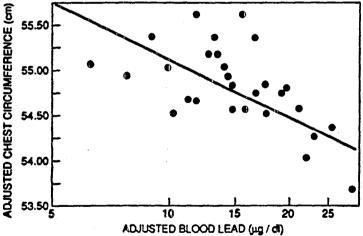


FIG. 12. Adjusted chest circumference and adjusted blood lead levels for children ages 7 years and younger in NHANES II. Both chest circumference and blood lead level have been adjusted by regression for effects of age, sex, and all other variables significant at 0.05 level. Each point is mean chest circumference and mean blood lead level for approximately 95 consecutive observations, ordered by blood lead levels. Regression line reflects slope of coefficient obtained from multiple regression analyses of all 2671 points with no missing data (Schwartz et al., 1986).

Fig. 13. Multiorgan impact of reductions of heme body pool by lead. Impairment of heme synthesis by lead results in disruption of a wide variety of important physiological processes in many organs and tissues. Particularly well documented are erythropoietic, neural, renal-endocrine, and hepatic effects indicated above by solid arrows. Plausible further consequences of heme synthesis interference by lead are indicated by dashed arrows (EPA, 1986).

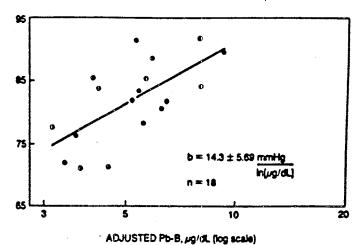


FIG. 14. Plot of adjusted diastolic blood pressure vs adjusted natural log of blood lead concentration in male bus drivers treated for hypertension with beta blockers. Adjusted for age, age², race, body mass index, and frequencies of caffeine, alcohol, and tobacco use. Diastolic blood pressure is the average of three measured diastolic blood pressures on each subject (Sharp et al., 1989).

between systolic blood pressure and blood lead levels, though small in magnitude, was statistically significant (P < 0.01). Analyses of data for men categorized according to blood level concentrations indicated increases in blood pressure only at lower blood lead levels; no further significant increments in blood pressure were observed at higher blood lead levels.

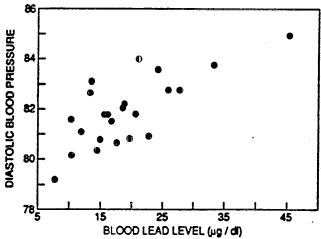


FIG. 15. Adjusted diastolic blood pressure and adjusted blood lead levels for males ages 20 to 74 from NHANES II. Both blood pressure and blood lead were adjusted by regression for the effects of age, age², body mass, and other significant variables. Each point represents the mean blood pressure and mean blood lead for 50 consecutive observations, sorted in increasing order of blood lead (Schwartz, 1988).

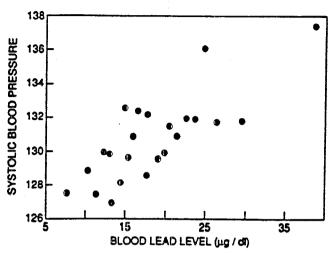


FIG. 16. Adjusted systolic blood pressure and adjusted blood lead levels from males ages 20 to 74 from NHANES II. Both blood pressure and blood lead have been adjusted by regression for the effects of age, age², body mass, and other significant variables. Each point represents the mean blood pressure and mean blood lead for 24 consecutive observations, sorted in increasing order of blood lead (Schwartz, 1988).

An ideal opportunity to separate the role of Pb from a wide range of potentially confounding nutritional factors was presented by the large data set from NHANES II, a random stratified sample of the U.S. population. Pirkle et al. (1985) described the results of their analyses of the data for 40- to 59-year-old white males from this survey population. After adjustment for age, body mass index, all measured nutritional factors, and blood biochemistry factors in a multiple linear regression model, the relationships of both systolic and diastolic blood pressures to blood Pb was statistically significant (P < 0.01). Figures 15 and 16 show the results of NHANES II analyses for adults ages 20-74 years from a review paper by Schwartz (1988).

The Pirkle et al. (1985) analyses incorporated additional variables with particular attention directed at the stability and significance of the Pb coefficient in the presence of nutritional factors and blood biochemistries. Their objective was to estimate conservatively the strength and independence of the relationship between blood pressure and blood Pb. Therefore, to provide an unusually rigorous test of the independent significance of blood Pb, 87 nutritional and biochemical variables in NHANES II were included in the stepwise regression. In addition, to account for possible curvilinear relationships, squared and natural logarithmic transformation of almost all these variables were also included.

The population mean blood Pb levels dropped by 37% between 1976 and 1980, due to reductions in the amount of Pb used in gasoline (Fig. 7). This much reduction in blood Pb in this population would be expected to result in a 17.5% decrease in diastolic blood pressure ≥90 mm Hg, a level used to define hypertension.

Considering the relatively unusual nature of the blood-Pb/blood-pressure relation (i.e., characterized by large initial increments in blood pressure at relatively

low blood Pb levels, followed by leveling off of blood pressure increments at high blood Pb levels), it is not surprising that it was not anticipated by results of studies in animals. Many animal studies emphasize results from exposures at higher dose levels, where results tend to be more definitive. The human results were, however, consistent with biphasic blood pressure increases observed in response to small PbB increases in the rat (Victery et al., 1982a, b; Perry et al., 1988) when rats were treated with low dose of lead. The unusual exposure-response relation may also account for the failure of earlier human studies to find consistent relations between blood pressure and blood Pb in study groups with mild-to-moderate elevations of blood Pb concentrations.

In summary, the use of a very large set of high-quality data covering a wide range of possibly confounding variables allowed a clean-cut determination of the effects of blood Pb on blood pressure for a relatively low range of blood Pb concentrations (5-35 μ g/dl). This association between relatively small elevations of PbB and elevated blood pressure may have significant public health impact because hypertension is a recognized risk factor for cardiovascular disease.

CONCLUSIONS

In 1943 Alice Hamilton looked back on her 33 years of experience with lead as an occupational toxicant and reminded us that there were many subclinical "manifestations of this protean malady." At that time, she remained concerned about subclinical effects in industrial workers. She could not have known that our failure to heed her doubts, expressed in 1925, that any effective measures could be implemented to protect the general public from the hazards of widespread use of leaded gasoline would lead, in this decade of the 1980s, to our current concerns about fairly well-documented neurobehavioral and developmental deficits in children throughout the country, or to our concerns for lead as a cardiovascular stress factor for adults.

Our most sophisticated tools for investigation, and our increased knowledge of exposure-response relationships for lead, would certainly impress Alice Hamilton if she could be with us again. However, in this era of emphasis on biological mechanisms of xenobiotic response, it is remarkable how little we now know about how chronic low-level lead exposure leads to such a remarkable array of toxic responses. Dr. Hamilton, trained in pathology, would surely be disappointed with our progress. On the other hand, Dr. Hamilton, our first full-time U.S. hygienist and occupational health physician, would, I think, be pleased with our recent progress in controlling the spread of lead and the consequent reduction in general population exposure. The virtual removal of lead from gasoline and canned foods, and the current attempts to reduce lead in drinking water show that we have learned some of the important lessons she tried to teach us.

ACKNOWLEDGMENTS

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- ATSDR (Agency for Toxic Substances and Disease Registry) (1988). "The Nature and Extent of Lead Poisoning in Children in the United States." USDHHS, Public Health Service, Atlanta, GA, July 1988.
- Baker, E. L., Jr., Folland, D. S., Taylor, T. A., Frank, M., Peterson, W., Lovejoy, G., Cox, D., Housworth, J., and Landrigan, P. J. (1977). Lead poisoning in children of lead workers: Home contamination with industrial dust. N. Engl. J. Med. 296, 260-61.
- Batuman, V., Landy, E., Maesaka, J. K., and Weeden, R. P. (1983). Contribution of lead to hypertension with renal impairment. N. Engl. J. Med. 309, 17-21.
- Bellinger, D., Levitan, A., Waternaux, C., Needleman, H., and Rabinowitz, M. (1987). Longitudinal analyses of prenatal and postnatal lead exposure and early cognitive development. N. Engl. J. Med. 316, 1037-1043.
- Bellinger, D., Needleman, M. C., Bromfield, R., and Nimtz, M. (1984). A followup study of the academic attainment and classroom behavior of children with elevated dentine lead levels. *Biol. Trace Element Res.* 6, 207-223.
- Bhattacharya, A., Shukla, R., Bornschein, R., Dietrich, K., and Kopke, J. E. (1988). Postural disequilibrium quantification in children with chronic lead exposure: A pilot study. *Neurotoxicology* 9, 327-40.
- EPA (1986). "Air Quality Criteria for Lead." EPA-600/8-83-028 U.S. EPA, Environmental Criteria and Assessment Office, Research Triangle Park, NC, June 1986.
- Hamilton, A. (1943). "Exploring the Dangerous Trades." Little-Brown, Boston.
- Harlan, W. R., Landis, J. R., Schmouder, R. L., Goldstein, N. G., and Harlan, L. C. (1985). Blood lead and blood pressure: Relationship in the adolescent and adult U.S. population. J. Amer. Med. Assoc. 253, 530-534.
- Kaye, W. E., Novotny, T. E., and Tucker, M. (1987). New ceramics-related industry implicated in elevated blood lead levels in children. Arch. Environ. Health 42, 161-64.
- Khera, A. K., Wibberley, D. G., Edwards, K. W., and Waldron, H. A. (1980). Cadmium and lead levels in blood and urine in a series of cardiovascular and normotensive patients. Int. J. Environ. Stud. 14, 309-312.
- Kromhout, D., and Couland, C. L. (1984). Trace metals and CHD risk indicators in 152 elderly men (the Zutphen study). Eur. Heart J. 5(Abstr. Suppl. 1), 101.
- Kromhout, D., Wibowo, A. E., Herber, F. M., Dalderup, L. M., Heerdink, H., Coulander, C. de L., and Zielhuis, R. L. (1985). Trace metals and coronary heart disease risk indicators in 152 elderly men (the Zutphen study). Amer. J. Epidemiol. 122, 378-385.
- McMichael, A. J., Baghurst, P. A., Wigg, N. R., Vimpani, G. V., Robertson, E. F., and Roberts, R. J. (1988). Port Pirie cohort study: Environmental exposure to lead and children's abilities at the age of four years. N. Engl. J. Med. 319, 468-75.
- Moreau, T., Orsaaud, G., Juguet, B., and Busquet, G. (1982). Plombemie et pression arterielle: Premiers resultats d'une enquete transversale de 431 sujets de sexe masculin. (Blood lead levels and arterial pressure: Initial results of a cross sectional study of 431 male subjects.) [letter]. Rev. Epidemiol. Sante Publique 30, 395-397.
- Needleman, H. L. (1984). "Comments on Chapter 12 and Appendix 12C, Air Quality Criteria for Lead" (External Review Draft #1). Available for inspection at U.S. Environmental Protection Agency, Central Docket Section, Washington, DC; Docket No. ECAO-CD-81-2 IIA.E.C.1.20.
- Needleman, H. L., Gunnoe, C., Leviton, A., Reed, R., Peresie, H., Maher, C., and Barrett, P. (1979).
 Deficits in psychologic and classroom performance of children with elevated dentine lead levels.
 N. Engl. J. Med. 300, 689-695.
- Needleman, H. L., Leviton, A., and Bellinger, D. (1982). Lead-associated intellectual deficit. N. Engl. J. Med. 306, 367.
- Perry, H. M., Jr., Erlanger, M. W., and Perry, E. F. (1988). Increase in the blood pressure of rats chronically fed low levels of lead. *Environ. Health Perspect.* 78, 107-111.
- Pirkle, J. L., Schwartz, J., Landis, J. R., and Harlan, W. R. (1985). The relationship between blood lead levels and blood pressure and its cardiovascular risk implications. Amer. J. Epidemiol. 121, 246-258.

- Pocock, S. J., Shaper, A. G., Ashby, D., and Delves, T. (1985). Blood lead and blood pressure in middle-aged men. "International Conference: Heavy Metals in the Environment, September, Athens, Greece" (T. D. Lekkas, Ed.), Vol. 1, pp. 303-305. CEP Consultants, Edinburgh, United Kingdom.
- Pocock, S. J., Shaper, A. G., Ashby, D., Delves, T., and Whitehead, T. P. (1984). Blood lead concentration, blood pressure, and renal function. Brit. Med. J. 289, 872-874.
- Rosner, D., and Markowitz, G. (1985). A 'gift of God'?: The public health controversy over leaded gasoline during the 1920s. Amer. J. Public Health 75, 344-352.
- Schwartz, J. (1988). The relationship between blood lead and blood pressure in the NHANES II Survey. Environ. Health Perspect. 78, 15-22.
- Schwartz, J., Angle, C., and Pitcher, H. (1986). Relationship between childhood blood lead levels and stature. *Pediatrics* 77, 281-288.
- Schwartz, J., and Otto, D. (1987). Blood lead, hearing thresholds, and neurobehavioral development in children and youth. Arch. Environ. Health 42, 153-160.
- Sharp, D. S., Osterloh, J., Becker, C. E., Bernard, B., Smith, A. H., Fisher, J. M., Syme, S. L., Holman, B. L., and Johnston, T. (1988). Blood pressure and blood lead concentration in bus drivers. Environ. Health Perspect. 78, 131-137.
- Sharp, D. S., Smith, A. H., Holman, B. L., Fisher, J. M., Osterloh, J., and Becker, C. E. (1989). Elevated blood pressure in treated hypertensives with low-level lead accumulation. Arch. Environ. Health 44, 18-22.
- Silva, P. A., Hughes, P., Williams, S., and Faed, J. (1986). Blood lead, intelligence, reading attainment, and behaviour in eleven year old children in Dunedin, New Zealand. J. Child Psychol. Psychiatry, in press.
- Victery, W., Vander, A. J., Markel, H., Katzman, L., Shulak, J. M., and Germain, C. (1982a). Lead exposure, begun in utero, decreases renin and angiotensin II in adult rats (41398). Proc. Soc. Exp. Biol. Med. 170, 63-67.
- Victery, W., Vander, A. J., Shulak, J. M., Schoeps, P., and Julius, S. (1982b). Lead, hypertension, and the renin-angiotensin system in rats. J. Lab. Clin. Med. 99, 354-362.
- Wang, J.-D., Shy, W.-Y., Chen, J.-S., and Yang, K.-H., (1989). Parental occupational lead exposure and lead concentration of newborn cord blood. Amer. J. Ind. Med. 15, 111-115.
- Weiss, S. T., Munoz, A., Stein, A., Sparrow, D., and Speizer, F. E. (1986). The relationship of blood lend to blood pressure in a longitudinal study of working men. Amer. J. Epidemiol. 122, 800-808.
- Winneke, G., Kramer, U., Brockhaus, A., Ewers, U., Kujanek, G., Lechner, H., and Janke, W. (1983). Neuropsychological studies in children with elevated tooth lead concentrations. II. Extended study. Int. Arch. Occup. Environ. Health 51, 231-252.
- Yaffe, Y., Flessel, C. P., Wesolowski, J. J., del Rosario, A., Guirguis, G. N., Matias, V., Degarmo, T. E., Coleman, G. C., Gramlich, J. W., and Kelly, W. R. (1983). Identification of lead sources in California children using the stable isotope ratio technique. Arch. Environ. Health 38(4), 227-245.

Wilson

TRAPS AND ERRORS IN RISK ANALYSIS

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Risk analysis in its most general form is commonsense combined with arithmetic. The errors are errors of commonsense.

Rarely do we find errors of arithmetic, only failures to do the arithmetic. The fact that traps and errors exist should not, in my view, lead us to abandon risk analysis, but on the contrary, emphasizes the need for good risk analyses.

The first, and most often discussed error, is the demand for zero risk which appears in various forms. But while it is the new wisdom to regard the zero risk advocates as rabble rousers, or at best middle headed idealists, I want to emphasize that there has in the past been a role for an attempt to reduce the risk to zero. This was the case when the major risk of premature death was that of communicable disease.

This is brought out most clearly in a paper by Sir Richard Doll. Doll showed that by most simple measures, health is better now than it was 100 years ago and is improving. This is because there has been a steady reduction in disease. I can also

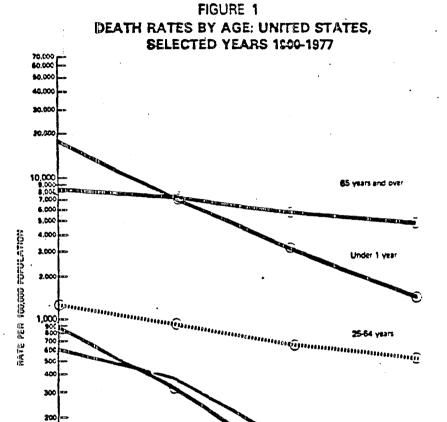
¹Doll, Sir Richard, "The pattern of disease in the post-infection era: national trends," Proc. R. Soc. Lond. <u>B205</u>, 47-61, 1979.

illustrate this by a plot of death rates versus time (Figure 1). The death rates are decreasing in all age groups except the one (15-24) where teenagers kill themselves with automobiles.

We can also go back over a longer period and look at life expectancy. In the year 800 A.D. life expectancy was about 28. It increased to 45 one hundred and fifty years ago, and is now 72 years for men and 76 for women (I personally am jealous of the women). The number of people surviving to a given age falls fairly slowly (Figure 2, but falls off sharply at age 70; an interesting age, because according to the nineteenth psalm, "the days of our years are three score years and ten" and nowadays compulsory retirement in the U.S. Does not begin until then. Death before age 70 can be considered premature and formerly premature death was mostly from disease

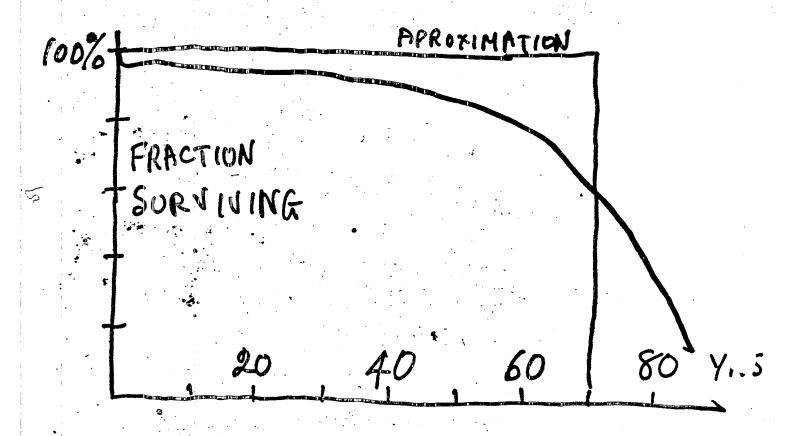
Diseases were removed as causes of death, not by medical advances, but by technical and scientific ones. An Oxford historian has pointed out the influence of the drainpipe (for main drainage) in the European history of the early 19th century. Chlorination of drinking water also played a major role. We must not, therefore, turn our backs on technology, but use it wisely. But there is an important corollary; the expense of reducing disease was moderate.

In each case there were a large number of dead bodies obviously attributable to a disease; and once the cause was recognized, a massive and rapid technological effort was made to remove the hazar completely. This led to a general view that once a risk of disease is recognized it is possible to complete eleminate it—and it should be completely eliminated. This, then, is a justification for the



BIOTE: 3977 gate are pravisional, sata for all etner years are final. Selected years are 1900, 1925, 1950, 1960. (for opt group 15-24 years only), and 1977.

BOURICE: National Center for Health Statistics, Division of Vital Statistics. $(HE\omega)$



zero risk approach.

The reason that the zero risk advocates are wrong is that the situation has changed dramatically. We have almost removed communicable disease in the Western world as a cause of death.

The second important error in a discussion of risks is a failure to recognize the changed nature of the risks which terminate our lives. The earlier risks can be called historical; the risk could often be calculated from historical data, and once the idea was suggested, the proof of causality was straightforward. are some people, and for politeness I will not refer directly to them, who have called for only regulating on these risks; for regulating only known measureable effects on health. If taken literally, this would prevent our controlling a large number of risks which are well worth reducing. We must recognize that risk is an expression of uncertainty. The uncertainty can arise in two ways; we can for example believe that cars kill people who cross the road, yet be uncertain that an individual is killed; or we can be unsure whether a new technology will ever kill anyone or not. The new risks of society are for new technology, about which we must speculate. It is improper to say "we do not know if there is a risk of air pollution at present levels." If we do not know--there is a risk, but the magnitude of the risk may be uncertain.

These two errors are at the root of our present discussion about the Clean Air Acts. On the one hand some people still want zero risk, forgetting that air pollution is not a communicable

disease and zero risk makes no sense, and on the other hand others are unwilling to regulate until dead bodies can be counted and reliably attributed to the source.

No risk analysis is perfect. In those I have reviewed, and Crouch and I discuss a number in our book on Risk/Benefit Analysis2, the most important is omission of an important risk. It is foolish to compare risks of nuclear power and coal without mentioning the risk that either may contribute to war; the one perhaps by making nuclear fuel more easily available, the other by making energy more costly. We must insist on putting numbers on each and every risk we can, but there are some risks that cannot be easily expressed in numerical terms. If the numerically expressed risks are properly discussed, these other risks will be highlighted; all too often they are ignored. For example, a 400 page report on LNG safety ignores questions of sabotage. Instead of saying so in the abstract, introduction and summary, the sentence is hidden in the middle. Yet for LNG and LPG facilities it is my considered view that the siting should be governed by the possibility of sabotage. 3

Samuel Johnson once wrote that "Round numbers are always false" and a risk analysis without a discussion of uncertainty can be false. As I noted before, it is in the region of uncertain risks—risks of a consequence which we are not even sure exists—

²E.A.C. Crouch and Richard Wilson, Risk/Benefit Analysis, Ballinger Press, Cambridge, MA, 1982.

³Richard Wilson, Testimony to Energy Facilities Siting Council, Massachusetts (1979).

that a risk analysis is the most important. In this case, however, it is vital to state the assumptions—early and often, as it used to be said about instructions to Cook County voters. But it must not be thought that an uncertain number is useless. Dr. Samuel Epstein and Samuel C. Florman in two separate articles in the Technology Review^{4, 5} argue that the estimates of risk of exposure to vinyl chloride at low doses vary by a factor of 100,000, and are therefore useless. They are wrong on both counts. Estimates vary by an infinite factor; some scientists argue that the risk is finite, others that it is zero. Any finite number divided by zero gives infinity (not 100,000).

Yet risk analysis can be useful; as of 1981, 82 cases of liver angiosarcoma had been attributed to occupational exposure of vinyl chloride world wide. These were due to past high exposures over a 20 year period. Liver angiosarcoma is a rare cancer, and few attributable cases would have been missed. Allowing for some cancers still in the latency period, cancers at other sites in the body, and cancers from exposures in the general environment, I find a maximum of 1000 over 20 years from past exposures. Exposures have now been reduced 1000 fold, and most scientists would agree that the number of cases will fall at least linearly to 1 every 20 years worldwide, and I believe no liver angiosarcoma has been attributed to exposures in the last 5 years.

⁴Samuel Epstein, "Cancer inflation and the failure to regulate," Technology Review, Dec./Jan., 1980.

⁵Samuel C. Florham, "Living with technology: tradeoffs in paradise," Technology Review, Aug./Sept., 1981.

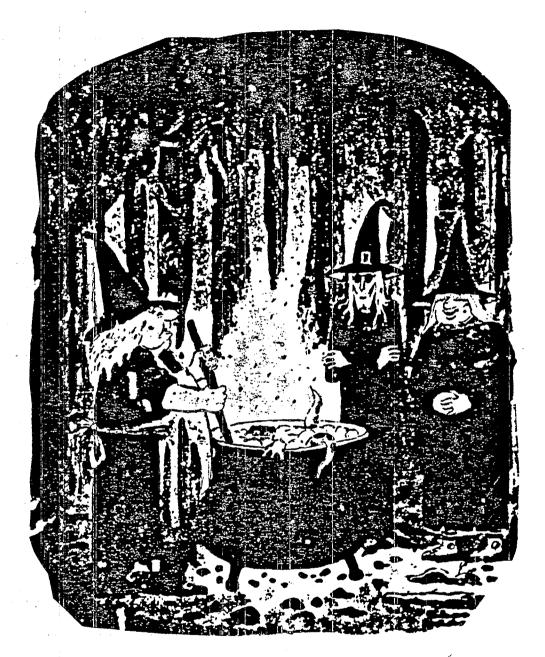
A number of people argue that natural foods are better and our problems of cancer and so on arise from artificial chemicals. It is conventional wisdom to ridicule this. This ridicule is illustrated in a New Yorker cartoon (Figure 3) showing that natural ingredients were used for witches' brews as well as for honest men's sustinence. Indeed, I like to point out to our local health food store that peanuts dried in the sun dry more slowly than those dried artificially and develop more molds and therefore have higher concentrations of aflatoxin Bl. But it would be an error to ridicule the "health food nuts" without trying to see if there is a legitimate point in their favor. There is.

We have historical data on natural foods, and believe a major disaster is unlikely, whereas if a new chemical (such as thalidomide) is put on the market, thousands of people may be hurt before we know what the danger is because of a latent period.

But this is no excuse for turning our back on technology.

Natural phenomena may wipe out the human race, and got close to doing so in the black death. That particular risk is probably now eliminated by technology.

It is important to understand a proper flow of information in reaching decisions about risk. Risk analysis is an aid to a decision and should not be a decision in itself. It is a grevious error to confuse the risk analysis with the decision itself.



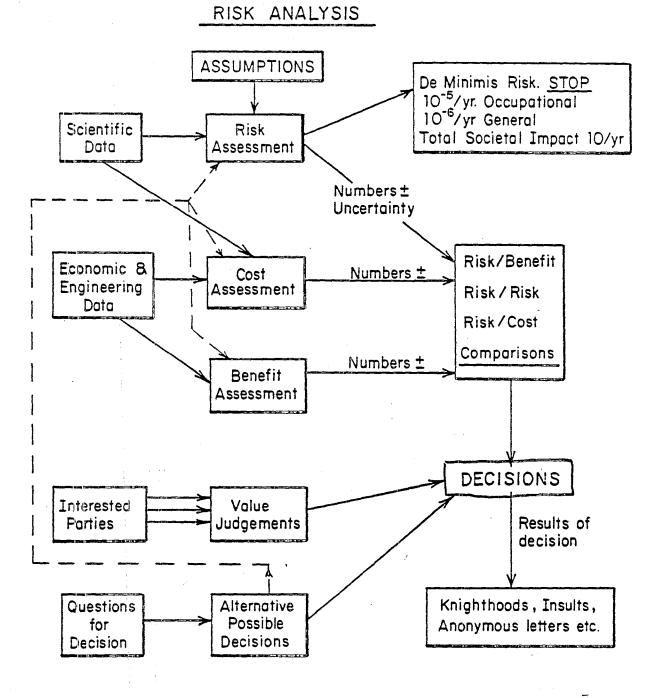
"It's going to be great! All natural ingredients."

I illustrate the flow of a discussion of risks in Figure 4. The information flows from the scientist to the assessor; to a comparison with costs and benefits to a decision maker (evaluator) who may be a bureaucrat, a politician or an ordinary citizen. All interested parties, unions, public, churches, industry, fishermen, etc. must be identified and these will have their own value judgments. Value judgments enter into the decision, but should not influence the assessment and comparison. Of course the assessor has to know the questions for decision, and some idea of the alternatives that are open to the decision maker in order to write down his assessment in such a way that the decision is properly illuminated. For this reason I put a dotted line between questions for decision and assessment.

The risk assessment is most useful when it is kept distinct in this way. The Carcinogen Assessment Group of EPA has been steadily improving in this regard; they usually quote the upper 95th percentile of the risk, but state also that it might be zero. They nowadays avoid directly supporting a decision.

I make here an analogy with the Anglo-Saxon legal system. The judge decides on questions of law; the jury--the assessors--decide questions of fact. The judge instructs the jury before they assess the facts as to what is legally relevant.

However the separation is sometimes deliberately broken as a historical example shows. In Cromwell's time, a law was passed making it illegal to kiss in public. Perhaps the law was sensible,



but there was a draconian penalty---death. However all juries violated the rules, and no jury would convict anyone accused of the crime.

Similarly if a group of assessors are asked an inappropriate question, or suspect that their answer may lead to stupid draconian measures, they may well decide not to state the true opinion. Thus if the question is merely "is this chemical a carcinogen" with no question of potency, I believe it is now inappropriate. If it is coupled with a draconian action of a complete unquestioning ban if the answer is yes, many scientists will refuse to play the game.

We can enter this diagram at any point; but usually it will be the decision maker who asks for an assessment. We must also be aware that if well done, a risk assessment may illuminate several different decisions. For example, the risk assessment for benzene may apply either in the workplace, or for the environment.

Errors often arise from not realizing that there are different constituencies in risk decisions and each constituency must be satisfied. It is an error to calculate the average risk to society, show that it is small and ignore it in spite of the large risk to an individual segment. I illustrate this by calculating the risk of being killed by a bear in Glacial National Park. According to the figures available to me, and as a risk assessor I accept this data, 2 people were killed in 1967; 1 person in 1975; and 3 people in 1980. That amounts to 6 people over about 15 years, or 0.4 per year. The Park Service informs

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me that the total number of park visitors is 1,500,000/yr; about 18,000 backpack campers/yr (25,000 permit nights); and about 1000 employees of park concessions. Of the 6 people killed, all were backpackers, and 4 were concession employees.*

The risk averaged over the whole U.S. population is:

$$\frac{6}{15} \times \frac{1}{220,000,000} = 2 \times 10^{-9}$$
 per year.

I do not expect the President of the U.S. to lose sleep over it. It is a de minimis risk.

The risk averaged over park visitors is:

$$\frac{6}{15} \times \frac{1}{1.500.000} = 3 \times 10^{-7}$$
 per year;

still de minimis by my criterion, but on the border of worth bothering about and indeed the park service have done little.

The risk as a fraction of backpack campers is:

$$\frac{6}{15} \times \frac{1}{18.000} = 2 \times 10^{-5}$$
 per year.

This is a voluntary risk worth reducing, but probably acceptable and, indeed, my wife and I accepted it a few summers ago (but we did take care; put bells on our packs and hung the food on poles).

The risk as a fraction of park concession employees is

$$\frac{4}{15} \times \frac{1}{1,000} = 3 \times 10^{-4} \text{ per year.}$$

This is now large, as large as the risk of driving a car to get to Glacier Park in the first place, and probably worth addressing by the representatives of this smaller group.

But this analysis leads, if we are not careful, to another trap. Why do you include in the denominator those who are not

^{*} This is based on oral statements only.

exposed? Because we may know no better. But we should go on reducing the size of the denominator until one reaches a logical trap. We should include in the denominator all those "at risk" and not only those who were killed. We get 6/6 or a risk of unity when we identify the group at risk as the group actually sleeping in the path of the bears and subsequently mauled. The denominator must be chosen so that the risk calculation has predictive power. To restrict the denominator too much takes away that power.

Bross, of the Rosswell Memorial Hospital in Buffalo, fell into this trap when discussing leukemia incidence. He restricted the group at risk to those who already had health problems which are precursers of leukemia. As shown by Bond⁶ his calculations have no predictive power.

Another error is to assume that a risk benefit analysis should be constant for all time. This omits the possibility of technology improvement. It is clear that the public wants risk to be reduced, and will not stand for additional risks being introduced to society—unless there is an obvious compensating risk reduction.

Therefore we must constantly search for ways of improving technology. I illustrate this by two examples.

From the earliest days it was known that x-rays cause skin cancer and in the 1920's it was found that radiation causes leukemia and in the 1930's and 1940's it was found that radiation causes a host of other cancers too.

⁶V. Bond, BNL report.

In the 1920's physicians pointed out the huge benefits of rapid diagnosis by use of x-rays, and said that the benefits out-weight any conceivable risk due to the x-rays. Of course they were right by a reasonable standard. This risk benefit comparison was particularly simple because the items were measured in the same units. X-rays save lives and these can be compared directly with lives at risk from the radiation induced cancer.

But the overall comparison of risk and benefit and the assurance that benefit exceeds risk is only the first question in a risk benefit approach. In the 1920's it was pointed out that the same benefit of rapid diagnosis by use of x-rays can be achieved with less risk: more sensitive x-ray film; image intensifiers; shielding against stray x-rays; and indeed it was not very expensive to do so. But these risks have only slowly been reduced, from many rads per x-ray in 1920 to 1 rad in 1950 to 5 millirads today. Why was the reduction slow?

Rachel Carson, in her much misquoted book, <u>Silent Spring</u>, agreed that pesticides were important and that the benefits of their use outweigh the risks. Again, if we think carefully, we can put at least some of the benefits in the same units as the risks; fewer pests means more food; more food means better nutrition; better nutrition reduces health risks. But Rachel Carson insisted it should be possible to have the same benefits with less risk by more careful use.

How do we ensure that we constantly address this question?

Carson, R., Silent Spring, Houghton Mifflin, Boston, 1962.

I believe that we must have a continuing decision process. The procedure in each of the above examples was to show that benefit > risk and the decision therefore was that the action should proceed. But in all cases of new technologies it seems appropriate to look further and ask whether we can reduce the risk with a modest cost.

In setting the air quality standards for moving sources (automobiles), Congress demanded a technology forcing approach. The standards were set progressively lower in the future and it was up to the automobile industry to find the technology to meet them. The industry screamed, but a Committee of the National Academy of Sciences chaired by Dr. Edward Ginzton of Varian Associates agreed that it was technically possible to meet this standard, and they are being met.

Is this technology forcing procedure the best way for technology improvement? Congress, after this success, thinks so. If we feel otherwise we must find a better way. I throw on the table for consideration the following idea. When any new product or process is accepted, there must be a fraction (1 to 10%) of the profits spent on a study of the alternatives to the actual action; other pesticides; less use (including how to restrain overzealous salesmen); better x-ray machines--and less x-rays, including how to prevent x-rays being taken merely to protect against liability in a negligence suit. This money could be paid by industry to NAS or a foundation to do this study.

I now bring to your attention four separate court and regulatory actions that recognize the importance of risk assessment and its more general extension, risk analysis.

- 1. The Court of Appeals, ⁸ in the case where FDA questioned the safety of Monsanto's plastic bottles made with an acrylonitrile polymer, stated that the administrator of FDA can ignore <u>de minimis</u> risks, notwithstanding the superficial rigidity of the Delaney Clause.
- 2. The U.S. Supreme Court decided in the benzene case that the Secretary of Labor for OSHA had to find (technical/legal term) that there is a significant health risk before proceeding and by quoting the one and only risk assessment before the court implied approval of risk assessment as a procedure for deciding whether a risk is insignificant or not. Chief Justice Burger stated that "inherent in this statutory scheme is the authority to refrain from regulation of insignificant or de minimis risks."

Although the Court quoted my testimony in this case, they failed to quote my successful effort at risk reduction. At the public hearing, the administrative law judge, and half the audience, were smoking and the room was filled with haze. I objected to being exposed to such dangerous carcinogens in the workplace. Now the hearing room is covered with numerous, large "No Smoking" signs.

⁸ Monsanto, et al., v. Kennedy, FDAO, 613 F 2nd 947 (DC Circuit)),
1979.

⁹American Petroleum Institute v. OSHA, et al., 581 F 2nd (DC Circuit), 1978; 100 S. Ct. 2844 (1980).

- 3. Now we have a consent order 10 between FDA and several cosmetic manufacturers. In this "FDA agrees to propose the utilization of scientifically accepted procedures of risk assessment and to raise the issue as to whether, in the view of the procedures, hair dyes containing 4-MMPD present a generally recognized risk to human health."
- 4. The FDA made a similar decision in deciding that the risk of lead acetate hair dyes (the Grecian formula) is insignificant.

As I look at a 5th case, the cotton dust case, it appears to be different. It has been argued that the Supreme Court decision is a repudiation of risk analysis. But we must note that "exposure to cotton dust represents a significant health hazard to employees."

The health hazard at current levels, acute byssinosis although reversible, is directly observable, unlike the effects of benzene at low doses which is merely inferred by extrapolation. I calculate with a very rough first guess using the numbers in reference 11 that the cotton dust standard proposed by OSHA saves cases of byssinosis (brown lung disease) and hence premature death at a cost of between \$50,000 and \$500,000 per case—less than the \$1 million per case often spent to reduce occupational disease, and \$10,000,000 to reduce occupational death and much less than the \$240,000,000 per calculated case I found in my calculations in the benzene case. Of course, we would like to understand the connection (if any) between

¹⁰ Carson Products, et al., v. DHHS, et al., Civil Action No. CV 480-71, U.S. District Court for the Southern District of Georgia, Sept. 1980.

^{11 101} Supreme Court Reporter, p. 2478, American Textile Manufacturers v. Donovan and National Cotton Council of America v. Donovan, 43 Fed. Reg., 27350, col. 1.

acute byssinosis and life shortening effects. Data on this is scarce and represents a challenge for risk analysts.

My cheerful tentative conclusion is that the Supreme Court behaved with commonsense in both decisions. If OSHA had perfomed a reasonable risk-benefit analysis it is not obvious that they would not have reached the same decision, or decided to lower the standard for cotton dust even lower than 200 $\mu g/m^3$ until they matched \$1,000,000 to \$10,000,000 per life--unless of course they found other, more serious secondary effects on the economy.

The point here is that, as far as I can tell, there was no widely accepted risk analysis presented in this case; and OSHA's decision to take prompt action to tighten the standard is then not unreasonable.

I now come to several errors that arise from inadequate comparisons of risks. For cancer risk calculations, Crouch and I¹² have been emphasizing the importance of including uncertainties in a risk calculation. I illustrate this by going over an argument I had with EPA's director of water quality standards at the Toxicology Forum in February 1981. I objected to his setting of a standard of 100 ppb for all halomethanes; drinking 2 1/2 liters of water containing chloroform every day for life can be shown to give a risk of 4 x 10^{-5} per year or 3 x 10^{-4} per life. This is based on several assumtions; that the dose response relationship is linear; that men in their lifetimes have as great a risk of cancer as animals in their lifetimes, when exposed daily to the pollutant

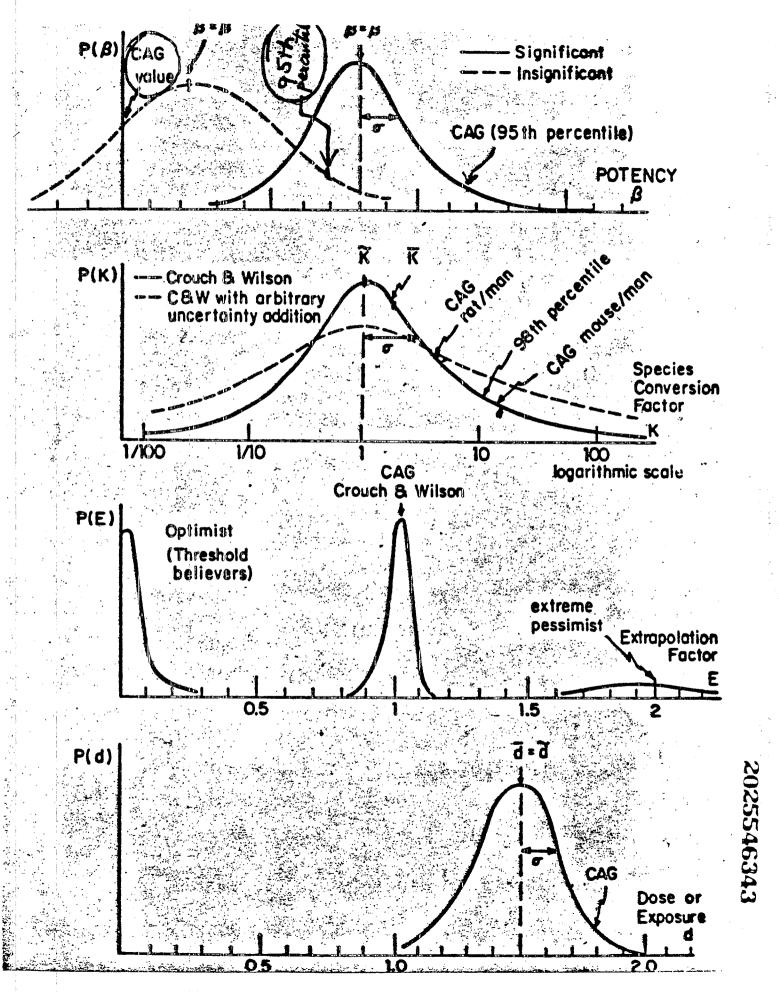
¹² Edmund A.C. Crouch and Richard WIlson, "Interspecies Comparison of Carcinogenic Potency," Journal of Toxic. and Environ. Health, 1979. Edmund A.C. Crouch and Richard Wilson, Journal of Risk Analysis, 1, 1 (1981).

with the same fraction of body weight.

methanes are more toxic and more mutagenic; by skin painting tests more carcinogenic. The exact amount is uncertain, but it is hard to see how the risk could fail to be greater at equivalent exposures, and therefore the standard should be lower. Similarly, tribhlorethelene and perchlorethelene are less toxic, and less carcinogenic (if carcinogenic at all) and the allowable exposure might reasonably be greater—or at least it should be explained why it is not.

We can reintroduce the zero risk error in a new form if we demand too low a risk, and demand too conservative a way of calculating it. FDA has proposed in a discussion of accidental food additives such as DES, that risks less than 10^{-6} per lifetime (1.4 x 10^{-8} per year) be ignored as de minimis and by implication other risks should be regulated. This is a very low number. Moreover there are very conservative rules proposed for calculation. By simple extension of these rules, I would find that many municipal drinking water systems in the U.S. have risks of 10^{-4} per year. It is clear that the FDA rule cannot be applied to all situations, and it therefore needs more discussion to show just where it should be applied (if at all). At the present time, most agencies are inconsistent without saying so.

In the next two figures I show how this comes about. The risk, according to our approach, has 4 factors:



 $R = \beta d K E$

 β is the carcinogenic potency defined as the slope of the relation connecting tumor incidence and dose;

d is the dose (or exposure);

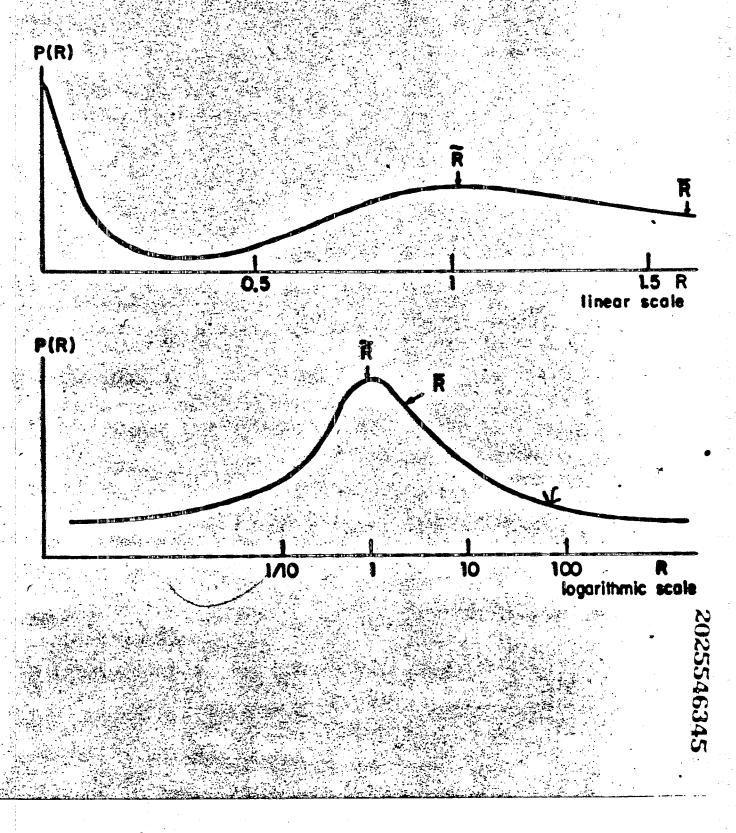
K is an interspecies conversion factor. We take a probability distribution for this, centered around unity when animal and human risks are compared for equal lifetimes and doses are compared as a fraction of body weight.

E is an extrapolation factor; to relate the risk at high doses (measured in animals) to that at low doses. E = 1 in the present conventional wisdom, but if we believe in a threshold we can put E = 0.

In Figure 5 I show a calculation of β (in animals) from data, and the spread of the probability distribution $P(\beta)$ around the best value β is given by statistics. The solid line is when the chemical is identified as a carcinogen, the dotted line when it is not because β is not 3 standard deviations from zero. CAG take the 95th percentile point as shown for the solid line, but take 0 for the dotted line. We believe this is inconsistent. It leads to regulatory hiatus, improper signals to industry, and improper comparison of risks.

We see this by noticing that the data for saccharin looked like the dotted line before 1977 and that for formaldehyde before 1981.

Neither chemical was regulated. Suddenly, on April 15, 1977, the FDA declared saccharin that is a carcinogen when new data became



available, and when in 1981 unpublished data from an NYU study became available, formaldehyde became a carcinogen and strongly regulated.

In each case there were prior indications of probable carcinogenicity. The regulatory hiatus would have been avoided if both chemicals had been regulated on the basis of the 95th percentile of the risk even before the experiments became sensitive enough to have statistical significance. Moreover, under the present CAG procedures, it is to industry's benefit not to perform a sensitive experiment, and change a chemical's status from no regulation to stringent regulation. Under our suggestion, the chemicals would be regulated in both cases, and shrinking the statistical error might actually reduce the impact of the regulations.

For K, we take a broad probability distribution P(K), as discussed in reference 12. CAG take a fixed number for K, with no uncertainty, but since they compare animal to man on a surface area, rather than a weight basis, their number is close to the 95th percentile of our distribution as shown in the Figure.

The probability distribution for d presents no problems.

The combined distributions for the risk P(R) is presented in Figure 6; the top curve is drawn to a linear scale, the bottom curve to a logarithmic scale.

Now I distinguish between an accurate assessment, to calculate \tilde{R} or perhaps the average risk \tilde{R} , and a <u>prudent</u> assessment. A federal agency, such as EPA, has an obligation to protect the public, and will choose the upper 95th or 98th percentile of the distribution. This is proper. But in comparing risks, such as replacing

one pesticide by another, it would be <u>improper</u> to compare different moments of the risk distribution. If the 95th percentile is appropriate it should be calculated in both cases, <u>including</u> the case when the best value R or the mean value might be zero, or less. I hope we can get this point accepted some time. If and when it is, a corollary I predict is that it will be found impossible to consistently regulate risks below 10^{-6} per <u>year</u> $(7 \times 10^{-5}/1)$.

A much harder point is to realize that there is a risk, which should be calculated, even when a medical effect is not found (I noted this already in my discussion of error 2). Logically this is similar to the case when a chemical is not found to be carcinogenic. I note that a chemical cannot be found to be non-carcinogenic; only that its carcinogenic potency be less than a specified amount. Many papers by distinguised authors are logically imprecise here, and are therefore confusing. Formally we can express this by saying that \overline{R} may be 0, and \overline{R} may be 0 or even negative, but R_{95th} percentile is in such cases finite and often large.

I conclude by pointing out that as when we look at examples of the errors and traps that we can fall into when doing a risk analysis, we can avoid falling into them; moreover, in each example it becomes clear what a reasonable decision might be; whether to act or not to act; and if to act, who must reduce and control the risk.

In our bear example, it was not the president of the U.S.; the Park Service can provide information; but it is individuals who must act and probably the park concession operators must educate

their staff.

The proof of the pudding is in the eating. If risk analysis can help society in making decisions about risk—and in particular in reducing risk at reasonable cost—then risks analysis is worth—while. Otherwise it will be a useless intellectual exercise.

HEALTH RISKS
THE PERCEPTION OF REALITY AND
THE REALITY OF PERCEPTION

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INTRODUCTION

Life is a risky process. It ends with one of the risks evolving into a death-dealing hazard from which there is no escape. Some risks are voluntary, such as riding in an automobile, flying in an airplane or smoking a cigarette. Other risks are essentially involuntary, such as the risk of lung cancer from air pollution, breast cancer as a result of our genetic heritage, or the chance that we may be struck by a meteorite. Most risks have a probability much less than unity of materializing into an adverse health effect. One exception is the risk of death; only the cause and the time of death is uncertain. There is absolutely no uncertainty of whether the event eventually will occur.

Studies of the probability of disability and death from each of the many risks we are exposed to daily have matured collectively into the scientific discipline of Risk Analysis. One might assume that such information would influence our lifestyles. Persons using tobacco would quit, because the risk of lung cancer from this noxious weed is well understood both qualitatively and quantitatively. We all would be careful about driving and working around the house, because the two most likely places of serious accidents are streets and the home. We would eat thoughtfully and exercise regularly, and we would choose our occupation and recreation with safety in mind. One might assume that these decisions, and others like them, would be integrated into selections of options for healthy lifestyles. One might make that assumption—but for most persons, the assumption would simply be incorrect.

We often assume that providing information about health risks will cause people to change their behavior so that their risks are reduced. This assumption is fundamentally flawed. The flaw is that the relationships are very tenuous between information and education, education and behavior change, and behavior change and risk reduction. The "Health Education Paradigm" that proposes that information leads to risk reduction is suspect at best. At its

worst, it can pre-empt other, more successful approaches to helping people reduce risks. The real challenge of risk analysis and communication is to recognize that the processes of risk perception and reduction are far more complex than simply assimilating health risk data and making appropriate behavior changes as a direct consequence.

The complexity of risk perception often is underestimated by persons who try to convey information about health risks. Often these persons assume that simply providing "the facts" will lead to more intelligent decisions about health risks and their reduction. The success of these efforts usually is frustratingly disappointing. To influence decisions about health risks, one must deal with the perception, as well as the reality, of risks. To most of us, in fact, the perception of risks is more "real" than the reality of risks--often in spite of direct evidence to the contrary. The adage "People's perceptions of risks are often inaccurate" is a reductio ad absurdium. People's perceptions may be out of touch with reality as interpreted by others. But perceptions are a direct reflection of the way people think about health risks. These perceptions must be accepted as real and addressed as significant if attitudes and behaviors are to be changed and health risks reduced.

THE CHARACTER OF HEALTH RISKS

Individuals change and grow by taking risks. The same is true of societies. Neither individuals nor societies can thrive without taking risks. Risk aversion limits the potential of individuals and societies for growth and creativity. The issue is not how to avoid risks. It is instead how to choose among risks so that foolish ones are avoided and those that yield benefits worth seeking are selected consciously and intelligently. Occasionally risks can be reduced or eliminated through knowledge and appropriate action. Examples include control of infectious diseases through improved sanitation, reduced occupational hazards by design of safer work environments, improved vehicular safety by use of passenger restraints and decreased use of tobacco in many developed countries. However, no activity is completely free of risks. Even inactivity has risks, as evidenced by the emphasis on exercise as a preventive health measure.

THE PERCEPTION OF RISKS

The perception of risk is usually a rather irrational process. The presentation of purely objective information (ie, "the facts") is usually not an effective deterrent to irrational thinking or behavior. An approach from the premise that "If you only understood the facts, you would think like I do" is almost sure to fail. It is, in fact, usually viewed as arrogant and elitist. A more effective approach is to start from the way risks are perceived, and to work gently toward a more objective appraisal of reality, dealing with the perception of risks at each step. 1-4 There is no such

thing as "a misperception of risks". There is only the perception. The trick is to bring the perception into accord with the facts.

In addressing the perception of risks, one should recognize that often the actual risks are not even the issue. Frequently the issue is the freedom of deciding for oneself whether or not to accept the risk. The individual's right to decide, rather than the risk itself, is often the bigger issue. For example, most persons accept the not inconsiderable risks of riding in automobiles because their use is considered voluntary, and because they believe that they have some influence on the magnitude of risk, at least if they are driving. These same persons may actively oppose a hazardous waste disposal site or nuclear power reactor because they resent the involuntary imposition of risk, no matter how slight the actual risk may be. When risks are imposed in an involuntary manner, they often are interpreted as a moral and ethical dilemma, rather than a scientific issue. In such circumstances, risks cannot be addressed effectively by a simple presentation of data. Any effort to dismiss the perceptions and confine the discussion to facts makes the effort, and the presenter, irrelevant to the concerns of the audience. It also polarizes the issue and, not infrequently, the audience, into irreconcilable factions.

RISKS AND INDIVIDUALS

Most persons are reluctant to think objectively about health risks. Assuming total responsibility for decisions about health risks leads to an obligation to live with the consequences of those decisions. When people have all the available facts and are totally free to make decisions about risks, they cannot direct the blame for adverse consequences elsewhere. Most persons prefer that others (eg, governmental agencies or responsible individuals) establish rules and standards about health risks. In the absence of official rule-making bodies, community consensus and peer opinion often is looked to for guidance in decision-making. Then if adverse consequences occur, they can be attributed to inadequacy of the standards, lack of diligence in enforcing the rules, or the stupidity of friends and community leaders. That is, someone else is at fault and can be blamed for the consequences. Laying the blame at someone else's feet is particularly likely if the responsible entity is suspected of vested interests, bureaucratic bungling or inattention to detail. Being able to blame someone else if adverse effects occur greatly enhances the acceptability of risks.

Health risks are more acceptable if they are described in terms of "statistical" rather than identifiable victims. 5-7 For example, descriptions of injuries in an industrial or construction accident are more impressive than are statistics of the carnage on highways. The fascination of onlookers viewing a serious automobile crash is a manifestation of the sudden and shocking realization of the human tragedies hidden away in statistics about highway accidents.

Risks and benefits are almost always interpreted personally. Involuntary risks, no matter how small, must be accompanied by personal benefits if people are to accept them. Frequently, the decision to accept a risk reflects an asynchrony of risk and benefit. Activities where the benefits accrue quickly and the risks are deferred until later are usually more acceptable than those whose benefits and risks occur simultaneously. If the risks are immediate and the benefits delayed, then the activities may be rejected no matter how much the benefits may outweigh the risks.

Risks to children and to immediate future generations raise considerable alarm. $^{8-9}$ When one's family is involved, even deferred risks may be an unacceptable price for immediate benefits. However, if the risks are deferred to a remote future generation, most people feel little concern.

Often the benefits of an activity are shared among many individuals while the risks are assumed by only a few. This process is deemed acceptable only if the risks to the few are not inordinately high, irrespective of the collective benefit. Of course, those persons exposed to the risks must share in the benefits, or even receive some additional benefits such as salary bonuses (referred to as "hazard pay") or additional community resources (eg, water recreational activities provided by a dam for hydroelectric power).

RISKS AND SOCIETY

When life is comfortable, risks are less tolerable. Comfort implies the presence of a certain measure of benefits, and additional benefits may not justify extra risks. People living comfortable lives tend to be risk-averse and satisfied with present conditions. They tend to avoid risks even though the risks may stimulate growth and creativity. Risk aversity is apparent today in many developed societies, especially western Europe and the United States. Older people tend to be more wary of risks, perhaps because they are more experienced than younger persons and more conscious of their own mortality and vulnerability to disability. They may also be less ambitious in seeking benefits, because they have fewer people to share them with and less time to enjoy them. A society with a substantial elderly population tends to be less risk-taking than one dominated by young people. This trend is increasingly apparent in the United States, and presents a serious challenge to civic leaders faced with difficult issues that can be addressed effectively only through a fair degree of societal risk-taking in the near future. An economy based on services rather than industry tends to be less adventuresome and more cautious about risks. The economy of the United States is moving rapidly in this direction.

In a technologically complex society, many of the health risks are imposed involuntarily as a trade-off of risks and benefits. These risks are generally less acceptable than those which offer freedom of choice. The adverse consequences of involuntary health

risks, including the personal and public anxiety and societal unrest that they create, inculcate a desire for some type of compensation. The increasingly litigious culture of the United States is a direct reflection of this attitude.

THE RESPONSE TO RISKS

Risk implies a possible adverse consequence that may or may not materialize as an effect on health and wellbeing. Risk creates an aura of uncertainty, and people are discomforted by uncertain consequences and a fear of the unknown. As the uncertainty increases, the tolerance for risks decreases. As a consequence, health risk information is almost always interpreted emotionally rather than objectively.

Most persons, including representatives of the public media, have little understanding of probability, and tend to think in causal rather than probabilistic terms. To these persons, anecdotes and personal experiences are far more meaningful than statistics and epidemiology. Presenting health risk information in terms of quantitative probabilities of adverse consequences leads to confusion of the audience and frustration of the presenter. 10-11 Most persons simply do not (and refuse to) comprehend a statement such as "an increase of 1/100,000 in the probability of future cancer per millisievert of whole body dose equivalent from ionizing radiation." They tend instead to think causally, using only the information they can intelligibly extract from such a statement. this example, the tendency is to focus on the terms cancer and ionizing radiation and to conclude that exposure to radiation leads directly to cancer. And most persons have an anecdote or personal reminiscence that confirms this causal relationship. The perception may be irrational, but it is real and should not be discredited. Any attempt to discuss the health risks of radiation exposure should start from the perception and work towards a more rational understanding of the health risks of exposure to radiation.

The reality and the perception of health risks are often far apart. Communication that has the best chance of succeeding starts with the perception and works towards the facts. Any effort to discredit the perception as irrational and ignorant is interpreted as arrogant and unresponsive to the concerns of the audience. Persons trying to address health risks may prefer to deal in facts rather than ad hominens; to do so exclusively, however, only diminishes the effectiveness of the presentation and discredits the presenter.

THE ACCEPTANCE OF HEALTH RISKS

The likelihood of adverse consequences is important to persons exposed to health risks. Many other factors are also important. For example, the severity of outcomes and their proximity to exposure to risks influence the acceptability of risks. Death and major disability are more undesirable outcomes than are minor

inconveniences occurring as a consequence of health risks. 12-13 Pain and suffering caused by adverse consequences also influence the perception of risks and their acceptability. Risks that result in familiar events (eg, automobile crashes) may be more acceptable than those that produce uncommon consequences (eg, industrial disasters), even though the uncommon character of some events implies substantially lower risks. Greater attention and dismay is paid to events where multiple deaths and injuries occur, especially when they seem to be random occurrences (eg, airline crashes) or involve substances (eg, radiation and noxious wastes) that evoke a sense of fear and dread. Public attention is especially riveted on technologies such as nuclear power with a history of incidents attributable to human error. But without human intervention, some complex emerging technologies such as genetic engineering and robotically-controlled mass transit systems may ultimately be interpreted as too risky for societal development.

Risks are more acceptable if the degree of exposure to them can be controlled, if some possibility exists to reverse adverse consequences in the future, or if they produce consequences that are temporary rather than permanent. Peer pressure is often very influential in determining whether risks are accepted or rejected. This pressure is especially important for adolescents and young adults, but almost everyone is influenced to some degree by the opinions and attitudes of peers about health risks and their acceptability.

COMMUNICATING RISK INFORMATION

Communicators of information about health risks often adopt the wrong approach, 14-15 as exemplified by health risk messages that usually stress risks rather than benefits, and emphasize possible adverse effects rather than safety and the likelihood of no effects. For example, the air pollution index is quoted rather than the level of air quality; toxic wastes are mentioned rather than the byproducts of industrial developments; levels of discharge of noxious substances are described rather than their degree of containment; and the possibility of a nuclear emergency is focused upon rather than the safety record of the industry. Emphasizing the public's "need to know" certain information also misses the mark; the public has a "right to know" information relevant to its decisions about health and health risks.

People are influenced by the degree of media attention given to various risks and their adverse consequences. They also are affected by how recently media coverage was focused on them. Often the media has been accused of irresponsible presentation of information about health risks. Persons concerned about objective presentation of risks often implore the media to educate the public realistically about risks, rather than simply to report accidents and disasters in a manner that stimulates the public's prurient interests. Spokespersons of the media respond by disclaiming any obligation to educate; in their view, the responsibility of the

media is solely to convey information, not education, within the context of selling subscriptions and recruiting viewers. They recognize that safety and the avoidance of hazards and disasters are not news; neither are intelligent decisions and responsible behaviors. The media is a convenient target for blame by those frustrated with the difficulties of conveying health risk information and the disappointments of being unable to elicit rational attitudes and behaviors in response. This blame is misplaced, because it misinterprets the role of the media in our society, at least as it is understood by those responsible for it.

THE MEDIUM OF HEALTH RISK INFORMATION

In earlier times in our society, we assumed, somewhat naively, that industry would address any health risks associated with its activities. We also assumed that government agencies would ensure that this obligation was satisfied. In the more iconoclastic culture of the United States today, industry is viewed, somewhat cynically, as willing to cut corners at the expense of safety, and not infrequently government agencies are considered too bureaucratic and bungling to protect the public health and the welfare of individuals. Today activist groups of concerned citizens, and the threats of legal action, have largely supplanted trust in industry and reliance on government as deterrents to health risks. This distrust of industry and loss of confidence in government is undermining the nation's ability to move into new horizons coincident with a progressive economy, and is changing the orientation of society from a posture of stimulating new ventures to one of deterring them.

Today the credibility of health risk information depends as much on who presents the information as on what is presented. 16-17 Purveyors of such information need impeccable credentials, a reasonable level of knowledge, and no interest in the outcome other than the welfare of the community and the health and safety of persons in it. Health risk informants should be residents of the affected community so that their health, and that of their families, are influenced like that of everyone else in the community.

Persons knowledgable about health and the risks to it at both the personal and public levels are among the best candidates for these responsibilities. Educational, science and health leaders in the community are foremost among these resources. Physicians and scientists have an opportunity, and perhaps even an obligation, to become more involved as community resources in personal and public education programs about health risks. It is principally through their efforts that attitudes will be changed and behaviors altered so that more intelligent decisions will ultimately be made about health risks and their reduction.

REFERENCES

- 1. Cox GV, Strickland GD: Risk is normal to life itself. Am Ind Hyg Assoc 1988;49, A223-A227.
- 2. American Chemical Society: <u>Chemical Risk Communication</u>. Washington, DC, American Chemical Society, 1988, 1-28.
- 3. Henderson M, Dawson J: <u>Living with Risk</u>. 1987 British Medical Association. John Wiley & Sons, New York.
- 4. Covello VT, Sandman PM, Slovic P: <u>Risk Communication</u>, <u>Risk Statistics and Risk Comparison</u>: A Manual for Plant Managers. 1988 Chemical Manufacturers Association, Washington, DC.
- 5. Covello VT, von Winterfeldt D, Slovic P: Communicating scientific information about health and environmental risks: Problems and opportunities from a social and behavioral prospective, in Covello VT, Moghissi A, Uppuluri VRR (eds): <u>Uncertainties in Risk Assessment and Risk Management</u>. New York, Plenum Press, 1987, pp
- 6. Burger Jr. EJ: <u>Health Risks: The Challenge of Informing the Public</u>. Washington, DC, The Media Institute, 1984.
- 7. Johnson B, Covello VT (eds): <u>The Social and Cultural</u>
 <u>Construction of Risk</u>: Essays on Risk Selection and Perception. 1987.
 Reidel Publishers, Boston.
- 8. Kasperson R: Six propositions on public participation and their relevance to risk communication. Risk Analysis, 1986;6, 275-282.
- 9. Fischhoff B: Managing risk perception. <u>Issues in Science and Technology</u>, 1985;2, 83-96.
- 10. Davies JM, Lee TR: Biases and attitudes in reactions to epidemiological and other risk assessments, in: <u>Epidemiology and Radiation Protection</u>. Paris, Agence pour L'Energie Nucleaire, 1988, pp 25-33.
- 11. Kahneman D, Slovic P, Turnsky A (eds): <u>Judgment Under Uncertainty: Heuristics and Biases</u>. 1982. Cambridge University Press, New York.
- 12. Hohenemser C, Kates RW, Slovic P: The nature of technological hazard. Science 1983;220, 378-384.
- 13. Covello VI: Informing people about radiation risks: A review of obstacles to public understanding and effective risk communication, in <u>Public Understanding of Radiation Protection Concepts</u>. Paris, Agence pour L' Energie Nucleaire, 1988, pp 8-64.
- 14. Ritenour ER, Hendee WR: Screening mammography: A risk versus risk decision. Invest Radiol 1989;24, 17-19.
- 15. Ruckelshaus WD: Science, risk and public policy. Science 1983;221, 1026-1028.
- 16. Dinmen BD: The reality and acceptance of risk. $\underline{\text{JAMA}}$ 1980;244, 1126-1128.
- 17. Sandman P, Sachsman D, Greenberg M, Gotchfeld M: Environmental Risk and the Press. 1987. Transection Books. New Brunswick, NJ.

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Communicating Risk Under Title III of SARA: Strategies for Explaining Very Small Risks in a Community Context

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Under Title III of SARA, companies must provide information about chemicals that they manufacture, store, or process. Communities will use data about potential accidental releases to develop local emergency plans. Data about routine chemical releases will be made available to the public on a computer data base. Simply having such data available does not ensure consensus about reducing potential chemical risks. Laboratory and field research are summarized, indicating that people tend to edit small risks to zero as being too small to worry about, or to adjust them imperfectly from an anchor equal to the potential loss. These results suggest recommendations for communicating about the risks posed by accidental or routine releases of chemicals.

Title III of the Superfund Amendments and Reauthorization Act of 1936 (SARA) is also called the Emergency Planning and Community Right-to-Know Act. Its purpose is to facilitate informed public participation in decisions about chemical risks—at the community level where these risks occur. Companies must provide information about hazardous and toxic chemicals that are present in their facilities as part of their manufacturing, storage, or processing activities. Title III covers both accidental and routine releases.

The availability of data per se does not ensure that every community will reach an easy consensus regarding what—if anything—should be done about the potential risks posed by these chemicals. Rather, different groups can be expected to have opposing reactions to this information. Apathy and/or denial may characterize one group's responses to this avalanche of information about the presence of chemicals and their routine releases. A typical resident might say: "This is information about chemicals that have been present in my community for years. Besides, safety practices and regulations now in place have reduced the amounts of these chemicals that get into the environment. I don't know anyone who got sick from these chemicals, and the companies using them provide lots of jobs here. I don't need this information, especially because it might lower the value of my property."

Public officials can be discouraged by this type of response because the Title III data can be used to protect communities from substantial risk in specific situations. For example,

the data could be used in a Local Emergency Plan to indicate that the appropriate evacuation routes depend on wind direction in case of an accidental release into the air; if residents are not aware of this, they may use evacuation routes that carry them into a pollution plume, rather than away from it. Another example is the case of communities where all companies are complying with their emission permits, but where the combined effect of these emissions may create potential "hot spots" in terms of annual emissions. If the residents ignore the Title III data, they may lose an opportunity to negotiate for changes that could reduce their potential exposure.

Public officials and business firms also are concerned about potential misinterpretation or even deliberate misrepresentation of chemical data. For example, the routine release data is reported in pounds per year; comparing 35,000 pounds of chemical X to 10,000 pounds of chemical Y may give the impression to the community and the media that chemical X represents a larger problem than chemical Y. However, this impression ignores important factors such as the comparative toxicities of X and Y and whether the release is likely to result in exposure. Special interest groups also could play on the apprehension that might be created by the sheer size of the numbers associated with the units in which the data must be reported (e.g., reporting 10,000 pounds may be far more frightening than the same information expressed as 5 tons). Public concern about the large number of pounds could lead to pressure for reducing emissions of substances much less likely to harm the community than smaller quantities of chemicals that are more toxic or more likely to result in exposure. Such considerations may result in a second group of citizens becoming overly concerned about some chemicals. The behavior of this latter group contrasts dramatically with that of the apathetic group.

When both the apathetic and concern reactions occur in the same community, there is likely to be conflict about interpreting risks revealed under Title III as well as about other risks. In this work, we use relevant research results to derive policy recommendations for communicating risks posed by either accidental or routine releases of chemicals in a community. The main objective of these recommendations is to assist government officials and members of Local Emergency Planning Committees (LEPCs) as they help citizens put the risks in context, that is, to raise community awareness of the larger risks without causing undue concern about the smaller ones.

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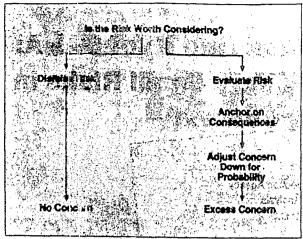


Figure 1. A model of risk judgement consistent with bimodal distributions of perceived risk.

Sara Title III--Background

Title III relies primarily on local planning and action. State commissions have been appointed to establish LEPCs, which use data relevant to potential accidental releases for preparing local emergency plans. The LEPCs must include elected state and local officials; policy, fire, civil defense, and public health professionals; hospital and transportation officials; as well as representatives from industry, community and environmental groups, and the media.²

Companies must participate in emergency planning if they have more than published threshold quantities of 366 substances listed as extremely hazardous. They must notify the LEPCs and their state commissions about releases of these chemicals that are above specified quantities. Companies must also submit information regarding inventories of hazardous chemicals to the state commissions, LEPCs, and local fire departments. They are not required to submit this information to the U.S. Environmental Protection Agency (EPA). The law became effective on October 17, 1987.

Prior to initiation of Title III, EPA had a Community Emergency Preparedness Program, which relied on voluntary submission of information so that communities could plan for chemical emergencies. Elements of this EPA program were incorporated into the Title III legislation. EPA and other federal agencies provide guidance and training for helping the LEPCs and state commissions cope with the deluge of information from companies that are required to report under Title III. For example, the National Response Team, which is composed of 14 federal agencies, has published guidelines for emergency response planning. The law required that the emergency plans be ready by October 17, 1988; they must be reviewed at least annually.

Data about routine releases of over 300 listed chemicals must be submitted annually both to the states and to EPA, beginning July 1, 1988. The threshold quantity of release for reporting purposes is 10,000 pounds per year for facilities using a listed chemical. Facilities manufacturing or processing a listed chemical have annual reporting thresholds that decrease to 25,000 pounds per year by July 1, 1990. These data will be made available to the public by EPA through a computerized Toxics Release Inventory. States also will make the routine release data available.

The Toxics Release Inventory will provide information regarding how much of each listed chemical is released from the facility into the air, water, and land. The quality of the data is expected to be variable, because there are no monitoring requirements in the legislation. A significant concern is that this data base will not have information that relates the emissions information to the likelihood and potential consequences of exposure. There is little overlap between

the chemicals that must be reported for emergency planning and those that must be reported for routine release. This is mostly because concerns about emergency releases (e.g., explosions, fires, acute health effects) often accompany different chemicals than the chemicals associated with chronic health and environmental effects that are of concern from routine releases. EPA is in the process of developing fact sheets that describe what is known about the consequences of exposure. The agency also is preparing a personal computer version of the Graphical Exposure Modeling System (GEMS), which is a model for combining routine emissions information with geographic characteristics to predict potential exposures.⁶

The legislation does not specify that LEPCs are responsible for interpreting the routine release data. However, the public may turn to the LEPCs, local and state health and environmental offices, state commissions, and even EPA officials, to help them understand the implications of Title III information. EPA recognizes that the LEPCs have the potential to be a community focus for managing both emergency and routine release risks under Title III.

Difficulties in Understanding Community Chemical Risks

To make recommendations regarding communication about chemical risks in a community, it is necessary to understand how people form beliefs about risks associated with chemicals and how these beliefs change. Figure 1 shows our model of risk judgement as a first step for explaining how the same risk information can lead some people to dismiss a risk as too small to worry about while others view the risk as a threat to themselves, their family, or their property. Several factors may affect whether a person worries about a particular risk. The first part of this section describes some of the empirical evidence supporting the model in Figure 1. The second part describes how various factors may influence possible outcomes under the proposed model.

A Model of Risk Judgement

Substantial empirical evidence indicates that people have difficulties evaluating small probabilities. McClelland et al. used laboratory experiments to demonstrate that subjects' bids (i.e., the amount they were willing to pay) for insurance against a loss were approximately equal to the expected value of the loss—as predicted by economic theory^{7,8}—for probabilities of loss greater than approximately 0.1.9 However, subjects consistently bid more than the expected value of insurance for smaller probabilities of loss.

A more detailed examination of the results from the McClelland, et al. low-probability risk experiments is shown in Figure 2a. Economic theory predicts that people will bid the expected value of insurance for a particular risk, so that the ratio of bid to expected value of the insurance would be 1. However, in this experiment there were more bids at twice that ratio, and a substantial number at four times the expected value. In addition, many of the subjects bid zero for the insurance against a small probability loss. The results indicate that the distribution of the ratio of bids to expected value is bimodal.

A similar pattern can be seen in Figure 2b, which represents community beliefs about the risks associated with a Superfund site located in Monterey Park, California. As in the laboratory experiments, a substantial share of residents in the community judged the risk to be zero, while approximately 30 percent perceive the risk to be as high as one in one hundred. This is much higher than the scientists' estimates of potential risk from the Superfund site. For example, EPA's risk estimates imply an upper bound on nearby residents' risk of cancer from vinyl chloride of 1.67×10^{-4} . Although the results of these two case studies need further confirmation, they do suggest that the factors resulting in

bimodal distributions of perceived risk may be the same in the laboratory experiments and in an actual situation.

Bimodal distributions of risk perceptions may be explained by two cognitive processes: 1) dismissal^{10,11} and 2) anchoring and adjustment. 12-14 An intuitive explanation for these processes is that individuals confront so many low probability risks that it is impossible to develop an appropriate response for each one on the basis of analytical evaluation. One coping strategy is to dismiss those risks that are perceived to be below some threshold (i.e., the left side of the risk judgement model presented in Figure 1). In the McClelland et al. insurance experiments previously cited, fewer people bid for insurance as the probability of loss falls, so the amount of dismissal increases. For those who do think the risk is large enough to evaluate (i.e., the right side of Figure 1), the problem is how to decide on an appropriate level of concern (i.e., how much to bid to protect against a loss in the insurance experiments). The model indicates that people first anchor on the loss. That is, they focus on the magnitude of the potential loss. Then they adjust their concern (or bid for insurance) downward to reflect the fact that the loss will occur only some of the time. The cognitive psychology literature indicates that such adjustments nearly always are incomplete. 13,15,16 In the context of the insurance experiments, the concept of incomplete adjustment can be used to explain why the bids for insurance end up being larger than expected value (for respondents in the upper mode of the bimodal distribution).

For the previously cited insurance experiments, these cognitive processes for forming a risk perception can be shown in a simple equation:

$$B = L - (1 - e)(L - pL) = pL + e(L - pL) \tag{1}$$

where: B = the bid for protection against loss

L =the loss if the hazard occurs

p =the probability of loss, and

e =the adjustment factor

The equation indicates that people anchor on the potential loss L and adjust this amount toward the expected value of the loss, pL. An expected value model would predict the adjustment to be (L - pL), with e = 1. However, the term (L - pL)-pL) is modified by (1-e) because the adjustment is incomplete. Using the data from the insurance experiments, the model predicts the underadjustment factor to be only 2-3 percent. This error still distorts responses significantly for low probabilities because the difference between the anchor, L, and the expected value of the loss, pL, is very large for low probabilities. For example, if L = 100 and p = .01 then (L pL) = 99. If the underadjustment factor is 2 percent, then B = 2.98. Compared with the expected value pL = 1, this implies an adjustment error of 1.98. As the size of the adjustment needed becomes larger, so does the adjustment error (e.g., if L = 1000, (L - pL) = 990, and e(L - pL) = 19.8). The adjustment error seems especially large compared with the expected value pL, which will be small for low probabilities.

Given the bimodality that is likely to occur in a community's perceptions of low-probability chemical risks, the best strategy for the LEPC (or other responsible group) may be to help people approach the more appropriate mode of either "dismissal" or "concern," while recognizing that neither mode may be accurate. In order to select the most appropriate mode, the LEFC could use data provided under Title III, additional information about whether those releases might lead to exposure, and dose-response data. The risk communication strategies needed to help people get into a concern mode may differ from those needed to help them get into a dismissal mode.

The judgement of whether the concern mode is more appropriate than the dismissal mode is not a trivial issue. The true size of the risk cannot be determined because of the uncertainties associated with various steps of the risk esti-

mation process. Kisk assessments typically yield estimates of individual risk and estimates of the total number of people affected. However, other characteristics of risk also are important to the public. This makes it likely that there will be an element of value judgement in the LEPC's (or other responsible group's) decision about which mode is more appropriate.

Determinants of Dismissal versus Concern

Several factors may influence whether people dismiss a risk or evaluate it. Some of these factors are discussed below.

Framing of gains and losses. In their description of prospect theory, Kahneman and Tversky indicated that it is important to determine whether the risk being communicated will be viewed by community residents as an increase or a decrease in their level of risk. 10,17 People are more concerned about losses than about gains relative to the status quo. This means that a perceived increase in risk (a loss) will have a greater psychological impact than the same size reduction in risk (a gain). In common sense terms, going from thinking one is "safe" to believing one is "unsafe" makes an individual comparatively unhappier than going from thinking he is "unsafe" to believing he is "safe" makes him happier.

Because most community members probably are unaware of potential risk that must be reported under Title III, the data are likely to be viewed as a new risk and a loss in wellbeing. Thus, the risk is more likely to be evaluated than dismissed, and it is likely to be weighted more heavily because it is viewed as a loss. If the community is judged to need help getting into the dismissal mode, these considerations suggest that expressing risks in terms of the probability that "there will not be an accident" or that "there will not be adverse health effects" may generate less concern than expressing the risks in terms of the probability that "there will be an accident" or that "there will be adverse health effects." The reverse would be true if the community is judged to need more concern.

Another framing issue is the quantitative expression of risk. Although people have difficulty understanding low-probability risk, some results of the insurance experiments indicated that bids converged toward expected value when the risk was expressed as an aggregate across several time periods. ¹⁸ Subjects were told both that the probability of loss on any given round was 0.01, and that this meant the probability of at least one loss across 25 rounds was about 0.25. The resulting bids (to protect against any loss for the block of 25 rounds) showed less of a bimodal distribution, and they

were closer to the expected value.

These results suggest that it may be effective to express risks in terms of a longer time frame, such as a lifetime, at least for annual risks in the range of 10⁻² to 10⁻³. This strategy is less likely to succeed for smaller risks because the risk aggregated over an individual's lifetime still is smaller than the range of probabilities that most people understand. However, expressing aggregate (lifetime) risk to the neighborhood or community might have large enough probabilities to accomplish better understanding. For example, an individual lifetime risk estimate of 10⁻⁴ could be explained as one expected death over 70 years in a community of 10,000 people.

Experience. The amount and nature of prior experience is an important determinant of how much concern individuals will have about a risk. Risks that are familiar, for which the science is understood, and with which they have had prior benign experiences are more likely to be dismissed. Risks that are unfamiliar, not well understood, and for which there are no perceived benign experiences are more likely to generate high levels of concern. 19 For example, across 50 rounds in the insurance experiments using a probability of 0.01, the share of people in the concern mode dropped steadily with

benign experience until the adverse event actually occurred on the 33rd round. Then there was a sharp drop in the fraction of subjects in the concern mode, reflecting the gambler's fall acy that a low-probability event is less likely on the next round because it occurred on the previous round. During succeeding rounds, the share of subjects in the concern mode grew as fewer and fewer people felt comfortable dismissing the risk.

Many communities will recall only benign experience relevant to Title III, and tend to be in the dismissal mode. But in communities where there has been a chemical accident or an emergency release, a high share of the population may be in the concern mode.

Characteristics of the risk. Technical risk assessment identifies which adverse effect could occur and estimates its probability of occurrence and the number of people expected to be affected. These are the only parameters included in a risk assessment. However, individual's beliefs about other factors may influence whether they dismiss or express concern about a particular risk. There are several important characteristics of risk that cause people to have more concern. ^{20,21} The more serious and dramatic the consequences of a risk, the higher will be the anchor in the anchoring and adjustment process, so the final level of concern will be higher. Risks that are dreaded, that can affect many people at one time, and that are considered to be unfair or morally wrong tend to result in higher concern. ¹⁹

Personal characteristics. There is some evidence to indicate that personal characteristics affect risk perceptions. For example, people with more education, who are white, and

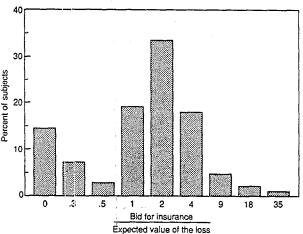


Figure 2a. Distribution of subjects' concern obtained from a laboratory experiment.9

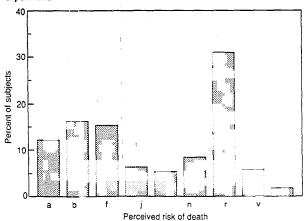


Figure 2b. Distribution of nearby residents' concerns about a Superfund site. Annual risk of death: a = no risk; b = one in 9 million; f = one in 100 thousand; j = one in 10 thousand; n = one in one thousand; r = one in one hundred; v = one in ten.

who tend to ask a doctor a lot of questions or read regularly about health have less concern about radon.²² Families with children, relatively young people, and women all tend to be more fearful of Superfund sites (and Superfund sites contain many Title III chemicals).⁹ For the Superfund sites included in this study, education, income level and occupation were not found to have an impact on risk beliefs of people living nearby, however.

Media attention. The need to maintain ratings or circulation gives the media an incentive for sensational coverage, especially when there is public controversy. Media coverage is likely to focus on those factors that encourage evaluation and lead to concern (e.g., a story reporting higher cancer rates in the area). The McClelland et al. research showed that frequent exposure to media reports about a Superfund site was significantly correlated with being in the concern mode.

Physical reminders. Risk judgements are influenced by perceptual cues. The more people are reminded of a risk, the more likely they are to be in a concern mode. Responses from 45 percent of the residents living near a Superfund site revealed that many of them perceived a dramatic decline in risk after the site was closed. No special closure activities had been undertaken to safeguard the community from the wastes already at the site, but the disappearance of physical reminders such as trucks and workers on the site may have been enough to change the community's risk beliefs. Increased perceptual cues regarding Title III could come from sirens and fire trucks signalling the emergency release of a chemical, or from odors that accompany routine releases. Chemical releases that are odorless and colorless are less likely to result in people being in the concern mode.

Recommendations

The following are recommendations for LEPCs and other groups that may be asked to interpret Title III data. Some of them are consistent with risk communication guidelines already available, but others are new.²³

- Identify and address community concerns. Effective risk communication is crucial if Title III is to lead to informed local decision making about chemical risks in a community context. Effectiveness requires recognition that community concerns may not be addressed by the usual components of risk assessment (e.g., residents may be worried by odors from a local chemical plant while experts may know that the odors are harmless, and not think it important to address the issue in discussions of Toxics Release Inventory data).
- Establish and protect credibility. Individuals communicating risk must be viewed as credible by the community. The diverse composition of LEPCs should demonstrate absence of bias toward any particular interest group. Care should be taken, however, because there are only limited public resources to support LEPCs' activities. The interests and available expertise of industry representatives on LEPCs may result in their having a large share of the committee's work. This could be perceived as self-serving. However, informed review by other committee members and the LEPC's state commission should ameliorate such concerns. Other neutral experts (from local colleges, laboratories, etc.) also may be called upon to reinforce the risk communication messages.
- Account for typical reactions to low-level risks. Because
 we observe fairly few fatal chemical accidents and chemical-related illnesses, nearly all of the Title III risks will
 have annual odds smaller than one in one hundred.
 Therefore, people will have difficulty understanding
 these risks and will tend either to dismiss them or to have
 a high level of concern about them, potentially resulting

- Recognize that characteristics of risk matter. A familiar, well known, and undramatic risk generates a lower level of concern than one with the same probability and consequence that is new, poorly understood, and dramatic. Even if people are convinced that the probability
- cause some differences in characteristics may cause people to reject the validity of the comparisons. For example, several voluntary risks are included in Figure 3, while people in a community may feel that Title III risks are imposed on them involuntarily. An alternative risk ladder could be developed, however, with better matching of characteristics of the comparison risks and the Title III risk.
- Treat the media as a legitimate partner. Providing complete and consistent information to the media will minimize the likelihood that they will become catalysts for inadvertently high levels of concern. In addition, access to experts can make it easier for reporters to develop an accurate but interesting story about a risk that the LEPC views as potentially large but that people are dismissing.

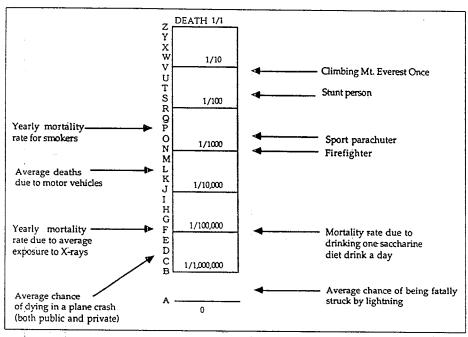


Figure 3. Example of a risk ladder, indicating risk for one year of exposure unless otherwise specified.9

and consequences are the same, they still often object more to a risk that is imposed upon them than to one voluntarily sought, one that affects many people at once rather than one at a time, or one that involves dread. This may indicate that the community really wants more of its resources devoted to reducing some risks compared with others that may have a higher probability or affect more people. Such preferences should be acknowledged when communicating about risk.

Use comparable risks. Risks should be expressed in concrete terms and put in perspective. Several suggestions are provided in a manual the Chemical Manufacturers Association has developed for plant managers. One approach is to match characteristics of the risks posed by Title III chemicals with characteristics of other risks with which people have more familiarity. An example of using comparable risks is presented in Figure 3, which shows actual risks associated with various activities. A Title III chemical could be placed on this risk ladder, next to the corresponding scientific estimate of risk. If the situation where the risk is being explained cannot accommodate the time needed to read and understand a risk ladder, one or two comparable risks can be described. Comparisons need to be used with caution, be-

Account for individuals' characteristics. For example, people with young families are likely to have higher concern about risks, especially compared with the elderly. Communications need to be targeted to subgroups, accounting for ways to reach them as well as making the message personalized to help them shift into the appropriate mode of dismissal or concern.

Disclaimer

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References

- Superfund Amendments and Reauthorization Act of 1986, PL 99-499, or 100 Stat. 1623.
- Superfund Amendments and Reauthorization Act of 1986, PL 99–499, Section 301(c).
- "Risk screening guide—interim final, Appendix F," U.S. Environmental Protection Agency Office of Toxic Substances, Washington, DC, 1988.

- "The Emergency Planning and Community Right-to-Know Act of 1986: questions and answers," U.S. Environmental Protection Agency Emergency Planning and Community Right-to-Know Information Hotline, Washington, DC, 1988.
 "The hazardous materials emergency planning guide," National Response Team, NRT-1, Washington, DC, 1987.
 "Right screening guide... interim finel Appendix C." H.S. Envi.
- "Risk screening guide-interim final, Appendix G," U.S. Environmental Protection Agency Office of Toxic Substances, Washington, DC, 1988.
- J. von Neumann, O. Morgenstern, Theory of Games and Economic Behavior, 3rd ed., Princeton University Press, Princeton,
- T. Tietenberg, Environmental and Natural Resource Economics, 2nd ed., Scott, Foresman and Company, Boston, 1988.
 G. H. McClelland, W. D. Schulze, D. L. Coursey, B. Hurd, J. R. Irwin, F. R. Boyce, "Risk Communication for Superfund Sites: An Analysis of Problems and Objectives," Draft report to U.S.
- An Analysis of Problems and Objectives," Draft report to U.S. Environmental Protection Agency, Office of Policy Analysis, Washington, DC, 1987.
 D. Kahneman, A. Tversky, "Prospect theory: an analysis of decisions under risk," Econometrica 47: 263 (1979).
 P. Slovic, B. Fischhoff, S. Lichtenstein, B. Corrigan, B. Combs, "Preference for insuring against probable small losses: Insurance implications," Journal of Risk and Insurance 44: 237 (1977).
- P. Slovic, "Influence of the Response Mode Upon Relative Importance of Probabilities and Payoffs in Risk Taking," in Proceedings of the 75th Annual Convention of the American Psychology chological Association, 1967.

- chological Association, 1967.
 A. Tversky, D. Kahneman, "Judgment under uncertainty: heuristics and biases," Science 185: 1124 (1974).
 H. Einhorn, R. M. Hogarth, "Ambiguity and uncertainty in probabilistic inference," Psychological Review 92: 433 (1985).
 D. C. Poulton, "The new psychophysics: six models for magnitude estimation," Psychological Bulletin 69: 1 (1968).
 S. Lichtenstein, P. Slovic, B. Fischhoff, M. Layman, B. Combs, "Judged frequency of lethal events," Journal of Experimental Psychology 4: 551 (1978).
 A. Tversky, D. Kahneman, "The framing of decisions and the
- A. Tversky, D. Kahneman, "The framing of decisions and the psychology of choice," Science 211: 453 (1981).
 J. Doyle, G. McClelland, W. Schulze, "Response Variation to Alternate Framings of Identical Low-probability Risk," University of Colorado draft report, Boulder, Co., 1988.

- 19. P. Slovic, "Informing and educating the public about risk," Risk
- P. M. Sandman, "Explaining Environmental Risk," U.S. Environmental Protection Agency Washington D.C., 1986.
- ronmental Protection Agency, Washington, D.C., 1986.
 22. F. R. Johnson, A. Fisher, "Conventional wisdom on risk communication and evidence from a field experiment," Risk Analysis,
- in press.
 23. V. T. Covello, F. W. Allen, "Seven Cardinal Rules of Risk Communication," OPA-87-020, U.S. Environmental Protection Agency, Office of Policy Analysis, Washington, DC, 1988.
 24. V. T. Covello, P. M. Sandman, P. Slovic, Risk Communication,
 P. Statistical Manufacture
- Risk Statistics, and Risk Comparisons, Chemical Manufacturers Association, Washington, DC, 1988.

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Socioeconomic Perceptions of the Future

INDUSTRIAL RISK PERCEPTIONS

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Abstract—The risks of occupational exposure to radiation need fuller and more explicit characterization. They also need a more developed quantitative comparison with more familiar occupational hazards.

To achieve this, some criterion is needed for establishing the amount of detriment one should attribute to different harmful effects, e.g., from accidents at work which cause death, temporary or permanent disability; from fatal and nonfatal cancers; from developmental abnormalities and any likely nonstochastic effects; and from a range of genetic defects.

No such criterion for comparing incommensurable kinds of harm can be scientifically defined, but one is essential if occupational exposure standards are to be put into perspective. A comparison of the frequency of fatal cancers and "severe" genetic defects with that of accidental deaths at work is admittedly incomplete.

One possible starting point is from a review of the average length of healthy life and activity lost as a result of nonfatal industrial accidents and some curable cancers, or of gross impairment during the course of an active disease or as a result of many types of genetic defect, or of life expectancy lost absolutely owing to fatal accidents and diseases. Estimates are discussed to emphasize the areas in which opinion is most needed to translate measures of risk based simply on total time lost into acceptable criteria of perceived detriment.

Standards of industrial safety are reviewed on this basis, both for risk from accidents at work and from radiation exposure, with evidence on the rate at which both types of risk are being reduced.

INTRODUCTION

STANDARDS of safety at work need to be better expressed and understood, particularly in their quantitative ranking in different industries. No industry is completely safe—some are very safe, and some are much less safe. This obvious statement may be adequate for a general view of occupational risk. It is quite inadequate when reviewing safety criteria in occupations involving exposure to agents such as ionizing radiation, asbestos, and probably many chemicals, for which no threshold for the induction of harmful effects can be assumed, for which the occupational risks must ordinarily be predictive rather than based securely on past records, and when the predictions for exposure at low doses must often be derived by inference from the frequency of effects observed at higher doses.

In such cases, the efficacy of protection criteria must be judged by comparing the total of all risks of exposure at given dose rates in relation to the total of all risks in other occupations. How do the risks of occupational exposure at a dose rate of 3 mSv y⁻¹ compare with those in an industry with an annual fatal accident rate at work of 3 per 100,000; and, more pertinently, how can qualitatively dissimilar risks be compared quantitatively?

If any such comparisons are to be convincing, they must fulfill three conditions:

- (1) All significant types of harmful effects should be taken into account, not only the fatal effects of occupational injuries and diseases.
- (2) Some factor which is common to all these types of harmful effect should be identified and its importance estimated in different occupations. One such factor is the total amount of time lost, both from normal health and activity and from the normal life expectancy, as a result of occupational accidents and diseases of different severities.
- (3) A simple numerical estimate of the total amount of time lost in this way as a result of these accidents or diseases is, however, obviously inadequate as a measure of the safety or risk of an industry. Very different weight should, and would, be attached to equal periods of time lost in different circumstances. A third step is therefore essential—to evaluate the weight that should properly be applied to different forms of harm, as assessed according to this criterion. No estimate of harm could be regarded as valid unless the perceived risk of different detriments was considered in some such way; although, the detriment attributed to different kinds of risk ought to be related to the magnitude of the risk, as well as to the type of harm involved.

Therefore, in comparing the safety of different industries, a first step could be to assess the length of time

20 per 10⁵ worker-y, the time losses due to fatal accidents

lost, from periods of good health and from average life span, because of the industries' characteristic occupational injuries and diseases, so that at least the magnitudes of these hazards can be compared.

INDUSTRIAL ACCIDENTS

For most types of occupational injuries, this is relatively simple. In many countries, records have been maintained for several decades of the annual frequencies, for example, per 100,000 workers at risk, of fatal and nonfatal accidents at work, the latter commonly including all those involving days off work.

Fatal accidents

In the case of fatal accidents, the annual loss of life expectancy can often be assessed directly, e.g., in years per 1000 worker-y, from the frequency of such accidents, the distribution of ages at which they occur, and the normal expectation of life at these ages among men and women in the countries concerned.

The mean age at which fatal occupational accidents occur among males varies somewhat in different industries, but it usually ranges within a few years of mean age of male workers in the industry (ICRP 1985, Table 9). In heavily industrialized countries, with a male life expectancy of longer than 70 y at birth, the mean loss of life expectancy per fatal accident at work is typically about 35 y (ICRP 1985, paragraph 41). In female workers, with a much lower frequency of accidental deaths, with a longer mean life expectancy, and often with a younger workforce, the value is probably somewhat higher, but it cannot usually be assessed reliably.

For an industry with an annual fatal accident rate of 3 per 100,000, and with a predominantly male workforce, fatal accidents would therefore contribute a total amount of time lost, by loss of life expectancy, in the region of 1 y per 1000 worker-y.

Accidents causing temporary disability

The total time lost due to nonfatal accidents can also often be reliably assessed in the case of accidents causing temporary disability. From the annual frequency of such accidents and from the mean resulting number of days off work, which may range in different countries and industries from about 15-30 working days (ICRP 1985, Table 11), the average annual (calendar) period of time lost (as assessed in terms of disability for work) can be determined.

In general, it is found that the total time lost per year in an industry—with many short periods of impaired health and activity—is broadly similar in amount to the annual loss of life expectancy due to fatal accidents in that industry. There is not, however, a simple proportionality between these two contributions to time loss in industries of different safety or risk. In the more hazardous industries, with fatal accident rates of more than about

Accidents causing permanent disability

contribution to perceived risk.

With accidents causing some degree of permanent disability, the position is less clear. It is easy to assess the total period of disability caused annually in an industry, given the frequency of new cases per year, the ages at which they occur, and given evidence on how frequently people so classed do remain permanently disabled. The main difficulty in any quantitative assessment, however, lies in the very wide range in severity of the disabilities which are recorded in different industries and countries, ranging perhaps from stiffness of a finger joint to loss of two limbs. It is evident that the detriment per year of a very severe disability, both to the worker and to his family, may be considered to approach that of a year's loss of life expectancy or perhaps, sometimes, even to exceed it. At the same time, most of the permanent disabilities recorded are much less severe, at least as judged by the average level of pension or compensation awarded, in comparison with the maximum level available for award. In some national records, the annual numbers of new cases of disability are expressed as an equivalent number of total disabilities, either in terms of some fractional assessment at the time of initial medical evaluation, or as an estimated number of days of complete disability.

In consequence, estimates of time loss due to permanent disabilities, either in terms of actual risk or perceived risk, depend very much on national or industrial policies in compensation and classification. Even when risks can be expressed in some more or less arbitrary equivalent to cases of maximum disability, or even when—as in several countries—the equivalence is based on the same anatomical criteria of injury in all industries, the relationship in detriment between a year of maximal disability and a year of lost life depends on the criteria of maximal detriment adopted nationally or in the industry. Given the rather sparse available data on the annual frequencies and rated severities of new cases of permanent disability, it seems likely that accidents causing such disability might be thought to involve a detriment of between half, and up to twice, that of fatal accidents in the same industry, but this question needs more attention.

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Detriment from all accidental injuries

Meanwhile, however, if permanent disabilities were judged to add a detriment about equal to that of fatal accidents in a rather safe industry (having an annual fatal accident frequency of 3 per 100,000 workers) and if the detriment from the temporary disabilities was considered to be small when compared to that from fatal accidents, the total detriment from accidents at work in this industry would be equivalent to about 2 y of substantial disability per 1000 worker-y, if equal weight were given to the total of all nonfatal accidents, as compared to that given to fatal accidents.

OCCUPATIONAL DISEASES—OTHER THAN RADIATION-INDUCED

In most industries, the total periods of health impairment and of life expectancy lost resulting from occupational diseases are small compared to periods of time lost owing to accidental injuries at work (ICRP 1985, Table 17A). The frequencies of disease are higher, however, in many forms of mining and tunneling, and in some chemical industries. In manufacturing industries also, the low time losses due to accidents may be significantly increased by those due to recognized occupational diseases; and in various occupations, the mortality from certain forms of cancer has been increased (ICRP 1985, Table 16).

In principle, the detriment due to occupational disease in any industry could be expressed in terms of health or life lost, as in the case of occupational injuries, although presumably with a need for differing weights attached to years of mild or severe disease or of loss of life. In practice, however, the severity of symptoms and limitation of activity are as difficult to assess in any quantitative way as are those in cases of permanent disability from accidents, and the durations of such symptoms of active disease or of life-shortening due to fatal conditions are not commonly reported.

There is, in any case, no constant component of diseases of varying severity in different industries, in the way that appears to hold for accidental injuries. For most industries, the contribution of industrial diseases to an index of occupational harm, based on years of substantial disability per 1000 worker-y, would be small compared to that from accidental injuries (ICRP 1985, Tables 17A and B).

RADIATION-INDUCED CONDITIONS

In most respects, the harmful effects of radiation exposure at low dose rates can be evaluated in terms of periods of life lost or impaired, as readily as can those of accidental injuries. Forms of impairment are more varied and complex than the simpler alternatives of lost life expectancy and short temporary disabilities due to accidental injuries, since they involve periods of active disease or detriment in the exposed or in their progeny, and periods of stress, disability and subsequent anxiety in the effective

treatment of those induced cancers which prove to be curable, as well as the losses of life expectancy resulting from fatal cancers and inherited diseases which cause premature death.

The need to form a considered opinion on the weight that should be attached to these is, however, in itself a reason for reviewing the estimated periods of impairment or lost life that may result from occupational exposure at any given dose rate and mode of exposure.

It is necessary, therefore, to consider the induction of fatal and of curable cancers, and of genetic effects of exposures received before conception of children. Non-stochastic effects are most unlikely to be caused by exposure under conditions in which both nonstochastic and stochastic dose limits to all organs are respected, with the possible exception of mental retardation in children if this effect is inducible without threshold by exposure of the mother during certain stages of her pregnancy.

Induction of cancers that cause death

The loss of healthy life due to the induction of fatal cancers involves periods of illness, commonly with severe disability before death and a variable amount of subsequent life-shortening. The former period is likely to average about 1 y, as indicated by medical evidence on the average length of survival from first diagnosis of the types of cancer, including leukemia, that are induced by radiation. The average amount of life-shortening in the exposed population can be assessed from estimates of the fatal cancer induction rate, the ages at which occupational exposures are found to occur, and the mean latencies from exposure to death that are assumed for radiation-induced fatal cancers.

The periods of illness from diagnosis to death, and of life-shortening due to the premature death, might be regarded as involving about equally severe detriment per year. The average periods of health or life lost for each fatal cancer induced can be estimated as about 1 y of severe illness and 14 y of lost life expectancy, if exposure was occurring throughout a working life from age 20 to 65. At a mean effective dose equivalent rate of 3 mSv y⁻¹, fatal cancer induction would then contribute a life-loss detriment of about 0.6 y per 1000 worker-y, taking 15 y of severe detriment for each fatal cancer induced, and an induction rate of 1.25 · 10⁻⁵ mSv⁻¹ as an average for males and females.

This estimate depends on the assumption of an "absolute risk" hypothesis, with a working population composed of both sexes equally and an average age of 40. It also assumes a slightly older mean age of exposure, as typically observed, and a mean latency to diagnosis of 13 y for leukemia and of 25 y for other cancers induced, which represent some 80% of all fatal cancers. On a "relative risk" hypothesis, the number of fatal cancers induced by exposure between ages 20 and 65 would be somewhat greater, probably by about 70% (NAS/NRC 1980, Table V.22) but with a greater proportion developing at older ages, so that the mean life-shortening for all fatal cancers

appears likely to be similar to that estimated on the basis of an absolute risk hypothesis (ICRP 1985).

Induction of cancers that prove to be curable

For most forms of cancer, it is much more difficult to estimate total rates of induction by clinical records or cancer registry data than to estimate mortality rates of the relevant cancers from epidemiological studies of death certifications. The number of curable cancers induced by radiation can probably be more reliably estimated on the conventional assumption that the cancers induced by radiation appear to resemble "naturally occurring" cancers of the same types in their clinical and pathological behavior. On this basis, the number of induced but curable cancers could be inferred from the recorded numbers of fatal induced cancers by conventional knowledge of the cure rate (or the 15-y recurrence-free survival rate) of cancers of the types, and in the proportions, found to be induced by radiation.

On this basis, the number of curable cancers estimated to be induced by (whole-body) radiation appears likely to be about twice the number of fatal cancers. This imbalance in numbers is due largely to the inclusion of skin cancers, for which the cure rate (of the types induced by radiation) is very high, and the cure is ordinarily very simple, the detriment involved in occurrence and cure of the cancer being correspondingly small. Of the forms of thyroid cancer found to be induced by radiation, the cure rate is relatively high—probably in the region of 90%. The detriment involved in cure in terms of symptoms, operative trauma and any subsequent treatment is ordinarily less than for cure of most other cancers.

For curable induced cancers as a whole, the detriment appears likely to be judged as substantial but as considerably less than that from induced fatal cancers, taking account of the relatively minor detriment involved in the cure of the majority of such cancers and the absence of a component of life-shortening in the group as a whole. A measure of detriment of 0.6 y per 1000 worker-y from fatal cancers alone could be regarded as increased to 0.75 y when including all cancer induction; or of 0.6 y or 0.9 y per 1000 worker-y in male and female sections of the workforce, respectively, taking account of the difference in both fatal and curable breast cancers and, to a lesser extent, thyroid cancers.

Induction of inherited abnormalities

Impairment of the whole life or of much of the life of descendants of those exposed to radiation involves quite different considerations from those associated with detriment in workers who are themselves occupationally exposed. In terms of the amount of harm resulting from any level of occupational exposure, however, and its assessment in terms of years of detriment and disability, it is obviously relevant to include whatever evaluation is possible for the genetic effects of exposure in these terms.

In this respect, the more recent reports of the United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR 1977, 1982) include estimates not

only of the frequencies with which different kinds of inherited abnormality are likely to be induced by radiation but also of the average lengths of life that are likely to be unimpaired, substantially impaired, or lost through premature death as a result of each type or group of inherited abnormalities.

Given the amounts of genetically significant occupational exposure received at ages before the conception of children, therefore, some estimate can be made of the total subsequent years of impaired health and loss of life expectancy due to inherited diseases in all progeny of those exposed. The "weighting" that would be given to such an estimate of the years of time loss in descendants, per 1000 worker-y of exposure, will not necessarily be the same as the weight that is thought to apply to years of disease, or of life loss, in those who are themselves exposed. It is, however, important to take account of any such inherited consequence of occupational exposure and to assess it in the light of its magnitude.

The genetic significance of any dose varies continuously with age as the probability of subsequent conception of children decreases with age. As an adequate approximation, it is sufficient to take as fully effective all gonad doses delivered before the mean age at conception of children, and as ineffective all such doses received subsequently. The mean ages at conception of children differ in different countries and differ substantially in men and women. Mean values in 41 countries are 30.6 (standard deviation [SD], 2.9) y in men and 25.9 (SD, 1.7) y in women (UN 1983, ICRP 1985, Table 21). The genetically significant proportion of any collective dose of occupational exposure therefore varies strongly with the sex and age distribution of workers and with the age of initial exposure, particularly in women. This proportion varies from 0.15 to 0.35 in groups of occupations in the United States (ICRP 1985, Table 22).

The detriment due to genetic defects induced in all generations subsequent to exposure was estimated by UNSCEAR as equivalent to 3.4 · 10⁻⁴ y of life impaired, and 2.9 · 10⁻⁴ of life expectancy lost, mSv⁻¹ of genetically significant irradiation of a parent. In a wholly male workforce of 1000, therefore, with equal numbers from age 20 to 65, with a mean age at conception of children of 30.6 y, and with a uniform mean dose rate of 3 mSv y⁻¹ from age 20, the annual genetically significant dose to workers would be that to the (240) workers younger than the mean age of conceptions, or 720 mSv. With a severe detriment, totaling 6.3 · 10⁻⁴ y mSv⁻¹, the inherited harm, as assessed on this basis, would contribute about 0.45 y of severe detriment per 1000 worker-y. For a female workforce, with a mean age at conceptions of about 26 years and with exposures equally from ages 20 to 65, the contribution would be about 0.25 y per 1000 worker-y.

These examples are, of course, expressed with an accuracy which is ridiculous as compared with the precision of the risk estimates on which they are based, let alone with the variability in age structure of different industrial groups. They can, however, offer some comparison between the carcinogenic risks to the individuals exposed

(of 0.6 and 0.9 y per 1000 worker-y in males and females) and the genetic risks to their descendants (of 0.45 and 0.25 y in males and females per 1000 worker-y); and could stimulate the necessary consideration of the relative weight that might be put on detriments to health and life in the exposed individual or in his and her progeny.

Detriment due to exposure during pregnancies

The detriment incurred as a result of exposures during pregnancies obviously depends on policies adopted with regard to restriction or continuation of radiation exposures at work during different stages of pregnancies, as well as on the age and sex structure of a workforce and on the frequency with which pregnancies are undertaken by full- or part-time workers in radiation-related industries. An upper limit to detriment can, however, be given if it is assumed that a worker does not restrict her pregnancies and that, in a non-expanding population, she will have, on average, two pregnancies during a period of employment starting at age 20; and that she works at constant dose rate throughout the whole of these pregnancies.

On this basis, one in 30 of all female workers would be pregnant at any one time, if there were equal numbers of women at all ages. However, as based on an actual age distribution of all women at work in England and Wales (U.K. Department of Health and Social Services 1970)—with 50% of the employed population younger than 30—this chance of a pregnancy being present in a member of the female workforce whether currently at work or not would be greater, with a probability of about 0.065 (ICRP 1977).

The likelihood that any form of harm might result from exposure of the developing child to low doses will depend upon the length of exposure time during pregnancy, and hence the size of dose received while the conceptus is sensitive to induction of that form of damage, and the probability per unit dose of inducing such damage during that time. For the induction of cancers which would occur during childhood or of harmful mutations in the developing gonads, which would be expressed in later generations, the period at risk corresponds to all or most of the pregnancy, although the risk per unit dose delivered during this period is likely to low, on the order of 1 or $2 \cdot 10^{-5}$ m/Sv⁻¹ in each case. For pre-implantation death of the conceptus, the risk per unit dose may be higher, as judged by findings in rodents, but the period of sensitivity, and hence the likely dose, is considerably shorter. For the one form of developmental defect which may be induced by low doses without threshold (namely, severe mental retardation), the induction risk has been estimated to be about $4 \cdot 10^{-4}$ mSv⁻¹ during an 8-wk period in pregnancy (Otake and Schull 1984).

Each of these forms of harm that may be caused by exposures of the conceptus has serious and, effectively, lifelong effects in the child or prolonged effects in genetically affected descendants. The total detriment, expressed in terms of lengths of life lost or of life seriously impaired, would amount to about 1.5 y per 1000 female worker-y exposed throughout all pregnancies at 3 mSv y⁻¹ (and

with a potential probability of a pregnancy of 0.065). Of this value, about 60% would be attributable to the developmental damage resulting in serious mental retardation, if this effect is in fact induced without threshold, although the epidemiological evidence does not exclude a threshold of some tens of millisieverts. Pre-implantation deaths and induced fatal cancers would each account for about 20% of the total estimate.

CONCLUSIONS

It should be emphasized that no simple catalogue of the frequency of different kinds of occupational injuries or diseases is sufficient in itself to define the relative levels of safety or risk of different industries, or the safety that they are judged to have by workers, by the public or by governments. Still less can any summation of years of detriment to health or loss of life give such a comparison, unless an appropriate weight is attached to years of different kinds or severities of detriment and probably to other factors such as the ages at which the years of detriment occur, and their occurrence in the exposed worker or in his immediate or remote descendants.

A merit of any attempt to formulate a unified index of total harm, however, is that it should provoke just such an evaluation of the importance that is attached to the different disabilities that contribute to occupational risks. And it will be a more considered evaluation than is obtainable if comparisons are based only on the kinds of effect which may be caused, regardless of the frequency with which they occur. Certainly the future evaluation of radiation protection criteria should take account of all the various forms of harm that may be caused by exposure to low doses, their relative frequencies, and the importance that is attached to their occurrences.

The same need for some unified estimate of the impact of different kinds of harm will be increasingly needed in work that necessarily involves some exposure to other potentially carcinogenic and mutagenic agents for which no entirely safe threshold can be assumed, as may apply in the case of asbestos and various chemical substances. A similar informed perspective on the relative risks of different agents and environmental conditions is equally or more urgently needed in regard to different sources and circumstances of public exposure.

Meanwhile, however, the present analysis, although obviously crude and capable of much improvement, does suggest the possibility of developing useful intercomparisons between dissimilar industrial risks. For example, the detriment associated with an occupational exposure rate of 3 mSv y^{-1} might appropriately be regarded as comparable in safety, as judged by periods of health and life lost, with conditions in an industry with a fatal accident rate of 3 per 100,000 workers at risk. In the case of male workers, the detriment is even less, as illustrated in the index of harm given below for an industry with a fatal accident rate of $3 \cdot 10^{-5}$ y⁻¹, and at a radiation dose rate of 3 mSv y⁻¹:

Years of health impaired or life lost per 103 worker-y

From injuries 2.2

| | Males | Females |
|---------------------|-------------|---------|
| From radiation | | |
| By cancer induction | 0.6 | 0.9 |
| By generic effects | 0.45 | 0.3 |
| During pregnancy | | <1.0 |

Currently, in the majority of all occupations recorded in the United States and the United Kingdom (Kumazawa et al. 1984, Hughes and Roberts 1984) and in 14 occupational groups reported by UNSCEAR (1982), dose rates are less than 3 mSv y⁻¹, although those in some forms of mining may reach about 10 times this rate. The mean rate for all potentially exposed workers in the United States was 1.1 mSv y⁻¹ (ICRP 1985). Similarly, the annual accidental death rate at work varies very widely in different industries (and countries) from less than 1 to over 100 per 100,000 at risk (ICRP 1985, Table 2). Manufacturing industries had an annual accidental death rate per 100,000 workers of 12.5 during the 1970s (ILO 1980) as the median value from 51 countries. More recently, 7.6 was the median (or 2.9 as the lower 25-percentile) of different manufacturing industries in eight highly industrialized countries (ICRP 1985, Table 7).

Any intercomparisons of risk should also take into account the rate at which the various risks are being reduced. In 40 occupational groups for which rates are available over a number of years (ICRP 1985, Tables 28AC), the recorded dose rates have been decreasing by a mean of 6.4% y⁻¹ (SE, 1.1). This rate of decrease in annual dose (and, therefore, of effective radiation risk) is somewhat faster than that of fatal accident rates at work, as recorded in 20 industrial groups in North America, Europe and Japan, for which the mean percentage rate of fall was 3.3% y⁻¹ (SE, 0.4) (ICRP 1985, Table 8A).

Any purely numerical comparison or summation of dissimilar kinds of risk must necessarily be artificial to a great extent. Certainly, however, a sound perception of industrial risks must depend upon an adequate quantitative assessment of the size of all major components of these risks, whether of trauma, disease or hereditary effects as well as on the more subjective assessment of their relative importance, not only to the worker, but also to the family and to the community. It should be a proper function of radiation protection to provide a realistic and comprehensive assessment of all significant aspects of the safety or risk of different occupations, and of different circumstances of routine or accidental exposure, and to present these assessments explicitly and quantitatively in the general context of the more familiar hazards of all other industrial activities.

REFERENCES

- Hughes, J. S.; Roberts, G. C. The radiation exposure of the UK population—1984 review. Chilton: National Radiological Protection Board; Report NRPB-R173; 1984.
- International Commission on Radiological Protection. Problems involved in developing an index of harm. ICRP Publication 27. Ann. ICRP 1 Publication 27. Ann ICRP 1(4)1-24; 1977.
- International Commission on Radiological Protection. Quantitative bases for developing a unified index of harm, ICRP Publication 45. Ann. ICRP 15 Publication 45. Ann ICRP 15(3)1-64; 1985.
- International Labour Organization. ILO year book of labour statistics. Geneva: ILO: 1980.
- Kumazawa, S.; Nelson, D.R.; Richardson, A. C. B. Occupational exposure to ionizing radiation in the United States: A comprehensive review for the year 1980 and a summary of trends for the years 1960-1985. Washington, DC: U.S. Environmental Protection Agency; 1984.
- National Academy of Sciences/National Research Council. The

- effects on populations of exposure to low levels of ionizing radiation. Washington, DC: National Academy Press; BEIR III Report; 1980.
- Otake, M.; Schull, W. J. In utero exposure to A-bomb radiation and mental retardation: A reassessment. Br. J. Radiol. 57: 409-414; 1984.
- U.K. Department of Health and Social Services. Digest of statistics analyzing certificates of incapacity (U.K.). London: Her Majesty's Stationery Office; 1972.
- United Nations Scientific Committee on the Effects of Atomic Radiation. Sources and effects of ionizing radiation: 1977 report to the General Assembly. New York, NY: UN; 1977.
- United Nations Scientific Committee on Effects of Atomic Radiation. Ionizing radiation. Sources and biological effects. 1982 report to the General Assembly. New York, NY: UN: 1982
- United Nations. UN demographic yearbook 1981. New York. NY: UN: 1983.

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Too Many Rodent Carcinogens: Mitogenesis Increases Mutagenesis

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clarification of the mechanism of carcinogenesis is developing at a rapid rate. This new understanding undermines many assumptions of current regulatory policy toward rodent carcinogens and necessitates rethinking the utility and meaning of routine animal cancer tests. At a recent watershed meeting on carcinogenesis, much evidence was presented suggesting that mitogenesis (induced cell division) plays a dominant role in carcinogenesis (1). The work of Cohen and Ellwein in this issue (2) is illustrative. Our own rethinking of mechanism was prompted by our findings that: (i) spontaneous DNA damage caused by endogenous oxidants is remarkably frequent (3) and (ii) in chronic testing at the maximum tolerated dose (MTD), more than half of all chemicals tested (both natural and synthetic) are carcinogens in rodents, and a high percentage of these carcinogens are not mutagens (4).

Mitogenesis increases mutagenesis. Many "promoters" of carcinogenesis have been described and have been thought to increase mitogenesis or selective growth of preneoplastic cells, or both. The concept of promotion, however, has been fuzzy compared to the clearer understanding of the role of mutagenesis in carcinogenesis. The idea that mitogenesis increases mutagenesis helps to explain promotion and other aspects of carcinogenesis (2, 5).

A dividing cell is much more at risk of mutating than a quiescent cell (4). Mutagens are often thought to be only exogenous agents, but endogenous mutagens cause massive DNA damage (by formation of oxidative and other adducts) that can be converted to stable mutations during cell division. We estimate that the DNA hits per cell per day from endogenous oxidants are normally $\sim 10^5$ in the rat and $\sim 10^4$ in the human (3). This promutagenic damage is effectively but not perfectly repaired; for example, the normal steady-state level of 8-hydroxydeoxyguanosine (1 of about 20 known oxidative DNA adducts) in rat DNA has been measured as 1 per 130,000 bases, or about 47,000 per cell (3). We have argued that this oxidative DNA damage is a major contributor to aging and to the degenerative diseases associated with aging, such as cancer. Thus, any agent causing chronic mitogenesis can be indirectly mutagenic (and consequently carcinogenic) because it increases the probability of converting endogenous DNA damage into mutations. Nongenotoxic agents [for example, saccharin (2)] can be carcinogens at high

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doses just by causing chronic mitogenesis and inflammation, and the dose response would be expected to show a threshold. Genotoxic chemicals [for example, N-2-fluorenylacetamide (2-AAF) (2)] are even more effective than nongenotoxic chemicals at causing mitogenesis at high doses (as a result of cell killing and cell replacement). Since genotoxic chemicals also act as mutagens, they can produce a multiplicative interaction not found at low doses, leading to an upward curving dose response for carcinogenicity. Furthermore, endogenous rates of DNA damage are so high that it may be difficult for exogenous mutagens to increase them significantly at low doses that do not increase mitogenesis. Therefore, mitogenesis, which can be increased by high doses of chemicals, is indirectly mutagenic, and seems to explain much of carcinogenesis (1, 4, 5). Nevertheless, the potent mutagen 2-AAF (3) induces liver tumors at moderate doses in the presence of only background rates of mitogenesis. Detailed studies of mechanism, particularly in the case of apparent exceptions, are critically important.

Causes of human cancer. Henderson and co-workers (6), and others (4), have discussed the importance of chronic mitogenesis for many, if not most, of the known causes of human cancer, for example, the importance of hormones in breast cancer, hepatitis B (7) or C viruses or alcohol in liver cancer, high salt or Helicobacter (Campylobacter) infection in stomach cancer, papilloma virus in cervical cancer, asbestos or tobacco smoke in lung cancer, and excess animal fat and low calcium in colon cancer. For chemical carcinogens associated with occupational cancer, worker exposure has been primarily at high, near-toxic doses that might be expected to induce mitogenesis.

Epidemiologists are frequently discovering clues about the causes of human cancer, and their hypotheses are then refined by animal and metabolic studies. During the next decade, it appears likely that this approach will lead to an understanding of the causes of the major human cancers (8). Cancer clusters in small areas are expected to be common by chance alone, and epidemiology lacks the power to establish causality in these cases (9). It is important to show that pollution exposure that purportedly causes a cancer cluster is significantly higher than the background of exposures to naturally occurring rodent carcinogens (4).

Causes of cancer in animal tests. Animal cancer tests are conducted at near toxic doses (the maximum tolerated dose, MTD) of the test chemical, for long periods of time, which can cause chronic mitogenesis (1). Chronic dosing at the MTD can be thought of as a chronic wounding, which is known to be both a promoter of carcinogenesis in animals and a risk factor for cancer in humans. Thus, a high percentage of all chemicals might be expected to be carcinogenic at chronic, near toxic doses and this is exactly what is found. About half of all chemicals tested chronically at the MTD are carcinogens (4).

Synthetic chemicals account for 82% (350/427) of the chemicals adequately tested in both rats and mice (4). Despite the fact that humans eat vastly more natural than synthetic chemicals, the world of natural chemicals has never been tested systematically. Of the natural chemicals tested, approximately half (37/77) are carcinogens, which is approximately the same as has been found for synthetic chemicals (212/350). It is unlikely that the high proportion of carcinogens in rodent studies is due simply to selection of suspicious chemical structures; most chemicals were selected because of their use as industrial compounds, pesticides, drugs, or food additives.

The human diet consists of thousands of natural pesticides (chemicals that plants produce to defend themselves) (4); we calculate that 99.99% (by weight) of the pesticides in our diet are natural. Of the natural pesticides that have been tested in at least one rodent species, about half (27/52) are rodent carcinogens. These 27

occur commonly in plant foods (10). We estimate that the average intake of these pesticides is about 1500 mg per person per day (4). By comparison, the average intake per day of residues of 100 synthetic pesticides is 0.09 mg per person per day (4). In addition, of the mold toxins tested at the MTD (including aflatoxin), 11 out of 16 are rodent carcinogens.

The cooking of food produces thousands of pyrolysis products, and we estimate that dietary intake of these products is roughly 2000 mg per person per day. Few of these have been tested; for example, of 826 volatile chemicals that have been identified in roasted coffee, only 21 have been tested chronically, and 16 are rodent carcinogens; caffeic aid, a non-volatile carcinogen, is also present. A cup of coffee contains at least 10 mg (40 ppm) of rodent carcinogens (mostly caffeic acid, catechol, furfural, hydrogen peroxide, and hydroquinone) (4). Thus, very low exposures to pesticide residues or other synthetic chemicals should be compared to the enormous background of natural substances.

In the evolutionary war between plants and animals, animals have developed layers of general defenses, almost all inducible, against toxic chemicals (4). This means that humans are well buffered against toxicity at low doses from both man-made and natural chemicals. Given the high proportion of carcinogens among those natural chemicals tested, human exposure to rodent carcinogens is far more common than generally thought; however, at the low doses of most human exposures (where cell-killing and mitogenesis do not occur), the hazards may be much lower than is commonly assumed and often will be zero (4). Thus, without studies of the mechanism of carcinogenesis, the fact that a chemical is a carcinogen at the MTD in rodents provides no information about low-dose risk to

Trade-offs. l'esticide residues (or water pollution) must be put in the context of the enormous background of natural substances, and there is no convincing evidence from either epidemiology or toxicology that they are of interest as causes of human cancer (4, 9). Minimizing pollution is a separate issue, and is clearly desirable for reasons other than effects on public health. Efforts to regulate synthetic pesticides or other synthetic chemicals at the parts per billion level because these chemicals are rodent carcinogens must include an understanding of the economic and health-related tradeoffs. For example, synthetic pesticides have markedly lowered the cost of food from plant sources, thus encouraging increased consumption. Increased consumption of fruits and vegetables, along with decreased consumption of fat, may be the best way to lower risks of cancer and heart disease, other than giving up smoking. Also, some of the vitamins, antioxidants, and fiber found in many plant foods are anticarcinogenic.

The control of the major cancer risks that have been reliably identified should be a major focus, and attention should not be diverted from these major causes by a succession of highly publicized scares about low levels of synthetic chemicals that may be of little or no importance as causes of human disease. Moreover, we must increase research to identify more major cancer risks, and to better understand the hormonal determinants of breast cancer, the viral determinants of cervical cancer, and the dietary determinants of stomach and colon cancer. In this context, the most important contribution that animal studies can offer is insight into carcinogenesis mechanisms and into the complex natural world in which we

REFERENCES AND NOTES

- 1. B. E. Butterworth and T. Slaga, Eds. Chemically Induced Cell Proliferation: Implications
- for Risk Assessment (Wiley-Liss, New York, in press).

 2. S. M. Cohen and L. B. Ellwein, Science 249, 1007 (1990).

 3. B. N. Ames, Free Rad. Res. Commun. 7, 121 (1989); C. G. Fraga, M. K. Shigenaga, J.-W. Park, P. Degan, B. N. Ames, Proc. Natl. Acad. Sci. U.S.A. 87, 4533 (1990). B. N. Ames, M. Profet, L. S. Gold, Proc. Natl. Acad. Sci. U.S.A., in press; B. N. Ames and L. S. Gold, ibid., in press; Med. Oncol. Tumor Pharmacother. 7, 69 (1990);
- B. N. Ames, Environ. Mol. Mulagen. 14, 66 (1989); ______, R. Magaw, L. S. Gold, Science 236, 271 (1987); L. S. Gold et al., Environ. Health Perspect. 81, 211 (1989). 5. J. E. Trosko, J. Am. Coll. Toxicol. 8, 1121 (1989); __ , C. C. Chang, B. V. Madhukar, S. Y. Oh, In Vitro Toxicol. 3, 9, 1990; Trosko has proposed that suppression of gap junctional intercellular communication in contact inhibited cells could lead to cell pre'iferation by cell death, cell removal, promoting chemicals,
- specific oncogenic products, growth factors, and hormones.

 6. B. E. Henderson, R. Ross, L. Bernstein, Cancer Res. 48, 246 (1988); S. Preston-
- Martin et al., in Chemically Induced Cell Proliferation: Implications for Risk Assessment, B. E. Butterworth and T. Slaga, Eds. (Liss, New York, in press).
 7. H. A. Dunsford, S. Sell, F. V. Chisari, Cancer Res. 50, 3400 (1990).
- 8. Current epidemiologic data point to these risk factors for human cancer: eigarette smoking (which is responsible for 30% of cancer deaths), dietary imbalances, hormones, viruses, and occupation. "[T]he age-adjusted mortality rate for all cancers combined except lung cancer has been declining since 1950 for all individual age groups except 85 and above" [National Cancer Institute, 1987 Annual Cancer Statistics Review Including Cancer Trends: 1950-1985, NIH Publication 88-2789 (National Institutes of Health, Bethesda, MD, 1988), p. II.3]. Although incidence rates for some cancers have been rising, trends in recorded incidence rates may be biased by improved registration and diagnosis. Even if particular cancers can be shown to be increasing (for example, non-Hodgkins lymphoma and melanoma) or decreasing (for example, stomach, cervical, and rectal cancer), establishing causes remains difficult because of the many changing aspects of our life-style. Life expectancy continues to increase every year 9. J. Higginson, Cancer Res. 48, 1381 (1988).
- 10. A search in foods for the presence of just these 27 natural pesticide rodent carcinogens indicates that they occur naturally in the following (those at levels over 10 ppm of a single carcinogen are listed in italics): anise, apple, banana, basil, broccoli, Brussels sprouts, cabbage, cantaloupe, caraway, carrot, casiflower, celery, cherry, cinnamon, cloves, cocca, coffee (brewed), comfrey tea, dill, egoplant, endive, femel, grapefruit juice, grape, honey, honeydew melon, horsendish, kale, lettuce, mace, mango, mushroom, mustard (brown) nutmeg, orange juice, parsiey, parsnip, peach, pear, pepper (black), pincapple, plum, potato, radish, raspberry, rosemary, sage, sesame seeds (heated), strawberry, tarragon, thyme, and turnip (4). Particular natural pesticides that are carcinogenic in rodents can be bred out of crops if studies of mechanism indicate that they may be significant hazards to humans.
- 11. This work was supported by National Cancer Institute Outstanding Investigator grant CA39910, by Nazional Institute of Environmental Health Sciences Center grant ES01896 and by DOE Contract DE-AC03-76SF00098. We thank M. Profet, S. Linn, B. Butterworth, and R. Peto for criticisms.

Has risk assessment become too "conservative"?

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Momentum is gathering to support the view that risk assessment, especially of carcinogens, tends to be skewed toward overestimating risks. Perhaps influenced by these arguments against overcaution, the Environmental Protection Agency has begun to reevaluate some of its procedures and lower some risk estimates. Adam Finkel of the Center for Risk Management cautions against hasty changes and calls for preserving the virtues of both good science and prudence.

uantitative risk assessment (QRA) is a science and an industry, and "risk numbers" are both its language and its currency. These numerical predictions of how many persons will suffer disease or death because of environmental exposure, or of the probability that an average person or a particular individual will succumb, now lie at the heart of environmental health regulation, particularly when it involves carcinogenic substances.

The recent controversy over daminozide (Alar) in apples, for example, centered around estimates generated by the Natural Resources Defense Council (NRDC) that as many as 5,300 of the current group of 22 million preschool children in the United States may contract cancer during their lifetime as a result of childhood exposure to Alar. This represents an estimated increase of 1 chance in 4,200 (above the background probability we all have of getting cancer) that Alar will cause cancer in a typical child. The NRDC also estimates that about 5 percent of preschool children ingest substantially more food containing Alar than the average child, and that these children face excess cancer risks approaching 1 in 1,000.

Experts and laypeople alike tend to ask two very different kinds of questions

when confronted with numbers like these. One set of questions involves ethical judgments about the acceptability of the stated risks; the debate over whether a risk of (say) 1 in 4,200 is too high will depend on personal and group judgments. These judgments concern the voluntariness of the risk, the magnitude of the probability (perhaps in relation to other environmental, occupational, or lifestyle risks we are more familiar with), the costs of eliminating or reducing the risk, and the real or perceived benefits of the risky product or activity. This acceptable-risk issue pits those who argue that no involuntary risk is acceptable if it can readily be reduced further against those who believe our society has become preoccupied with trivially small dangers. This is a vigorous debate, with divergent views expressed both within the expert community and the general public as well as between these two groups.

The other set of questions has to do with the believability of the estimates themselves. In contrast to the controversy over acceptable risk, the debate over whether risk numbers are credible has begun to resolve itself, at least among practitioners and expert observers of QRA. The general reader may be surprised that this group tentatively has concluded that risk numbers generally are not credible. The conventional wisdom of the experts is that these numbers are systematically skewed in the direction of overestimating risk, because the process used is in danger of being so "conservative"—so overly cautious—as to be a caricature of itself.

The intellectual and regulatory momentum is clearly on the side of the "revisionist" position, which seeks to replace conservative procedures because the status quo is allegedly causing alarmist and counterproductive reactions. The lack of resistance to some of these changes reflects the compelling evidence supporting some revisions, the fact that

the public may not be aware that subtle but accelerating changes are under way in QRA, and perhaps simply the natural swing of the pendulum in such matters. In my view, however, the rush to eschew conservatism is fueled in part by an uncritical acceptance of a set of flawed assumptions about QRA, so the pendulum swing may itself be counterproductive. I wish to offer a note of caution against hasty or piecemeal changes, and to suggest a new approach that may preserve the virtues of both good science and prudence.

The case against conservatism

The fundamental logical flaw of conservatism is that it can compromise our ability to make clear choices and set rational priorities. The strongest critics of conservatism view this distortion in the broadest possible terms; conservatism, they say, artificially inflates the relative importance of all proposed measures to reduce health and environmental risks. Some revisionists simply do not believe that the hazards of industrial pollution are as dire as the standard QRA procedures imply. But arguments that focus on the need to reduce existing risk numbers and redress the balance between risk and cost probably exacerbate the tension between the experts and the public, and may backfire. After all, a "realistic" toll of 530 extra deaths from Alar (if revision caused a lowering of this risk number by a factor of 10) might be no more acceptable to the public than a cautious estimate of 5,300 fatalities.

Therefore, a more reasoned and perhaps ultimately more successful argument against conservatism is that it creates imperceptible distortions among different risks, which we cannot redress simply by paying less attention to cancer risk reduction (or by agreeing that we are spending about the right amount even though we have exaggerated the size of the risks). The insidious aspect of consistently analyzing the "worst case" is that some cases are simply "worse" than others, in the sense of being less plausible or less likely to occur. For instance, one typical conservative shortcut is to assume

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Table 1. Some Potentially "Conservative" Assumptions and Alternatives Commonly Used in QRA

Assumption

Dose-response function is linear, so slope at low doses equals that at high doses

Response of most sensitive rodent species/ sex tested predicts human risk

All rodent tumors are predictive of human cancer risk

"Maximally exposed individual" (MEI) lives at plant or site boundary

MEI's exposure is determined by upperbound values of human uptake parameters (for example, breathing rate, water ingestion)

Concentration for all "not detected" samples is set as if it were just below the limit of detection

Possible alternative

Fit "sublinear" or threshold function to observed data

Pool the responses of all rodent groups tested

Discard data involving tumor sites and/or mechanisms that do not exist in humans

Obtain case-specific data on MEI

Use uptake parameters that represent the "average" human

Assume these represent instances of zero concentration

that the most highly exposed individual near a chemical plant or a hazardous waste site lives at the property boundary, and that he or she is downwind of the pollutant source 24 hours a day. In some cases, the resulting risk estimate will be quite conservative, if no one actually lives near the boundary or in the direction of the prevailing winds. In other instances, the estimate may be nearly correct. If the cancer risk estimate cited for the former situation was 1 in 10,000, and the estimate for the latter was 1 in 100,000, the former would seem more risky even though (unknown to the investigator) this estimate was less credible than its counterpart.

Steps toward revisionism

Perhaps influenced by these arguments against conservatism, the U.S. Environmental Protection Agency (EPA) has recently begun to reconsider some of the official risk estimates it developed in earlier years. To date, all of the proposed reevaluations have resulted in lowered risk numbers, generally by about a factor of 10. The most noteworthy of these cases involve methylene chloride (a solvent

used, among other things, to decaffeinate coffee), arsenic, and TCDD, also known as dioxin.

Potentially more farreaching than these ad hoc changes in specific risk assessments is EPA's September 1988 decision to rewrite its influential series of guidelines for quantitative risk assessment, which had been published in 1986. These guidelines determine which assumptions should be used under various circumstances, and indicate in general terms when professional judgment should supplant formulaic procedures. Although it is too early to tell specifically how the new guidelines will reflect what has been called the new era of post-conservative risk assessments, they may encourage the use of alternatives (see table 1).

Conservatism in perspective

A number of pervasive misperceptions about conservatism cloud the issue of whether risk numbers are credible and QRA procedures are reasonable. The following points refute three of the broad categories of misperceptions.

Existing procedures are not so unscientific or unreasonable. Critics tend to

malign different kinds of conservative assumptions with the same broad brush, failing to distinguish those that are gratuitous from those dictated by prudence or common sense. For instance, in contrast to the use of simplistic worst-case assumptions about exposure that could readily be refuted by reliable data, the commonly criticized use of the upper confidence limit when fitting a dose-response curve to animal data is a cautionary step of a quite different variety. This procedure recognizes that as we learn more about cancer potency, the truth may well fail to converge toward a lower result. To put it another way, suppose the owner of a baseball team approached one of his star players four days into the season and asked him to take a pay cut on the grounds that he was batting .050 at the time. The player would doubtless argue that he has always had about a 1 in 3 chance of getting a hit each time at bat, and that his current 1-for-20 string is too scanty a basis for claiming that that underlying probability has changed at all. By the same token, observing 5 tumors in a group of 50 rats does imply that each rat had about a 1 in 10 chance of getting cancer at that dose, but is only weak evidence against the more prudent assumption that the probability might be several times larger.

In addition, it is easy to carp about possible errors of commission in the QRA process without acknowledging that various errors of omission may make risk estimates more "nonconservative" for all or part of the human population. Of most significance, risk assessments commonly fail to account for the often-dominant indirect exposures (such as inhaling organic compounds that volatilize from hot tap water during showering and bathing) and for the likelihood that individual humans differ widely in their inherent susceptibility to carcinogenic stimuli (we currently assume that all humans are as homogeneous in their responses as are the inbred strains of rodents we test in controlled environments). Thus, the current mix of assumptions may contain certain margins of safety necessary to account for our inability to fully flesh out important considerations.

Beyond that, the common characterization of QRA as a "cascade" of conservative steps that yields progressively more unbelievable estimates may confuse issues of probability and magnitude. It is true that if one multiplies five estimates that each have only a 5 percent probability of being underestimates, the product will have much less than a 5 percent chance of being too low. However, many of the individual uncertainties in risk analysis are right-skewed; that is, the highest possible values in the "tail" are much greater in absolute terms than the more central values. The fact that extreme values are unlikely to occur becomes less and less important as the consequences of those values being true become greater. For example, the average indoor radon level in a sample of 5,000 homes in Pennsylvania was about 10 picocuries per liter (pCi/l) even though a randomly selected house had only about a 20 percent chance of containing more than 10 pCi/l. Decision makers and the public need to consider that while it is easy to ridicule a risk estimate for being exaggerated (in the sense of unlikely to be too low), such estimates may be more reasonable than less cautious ones.

Data do exist to validate some existing numbers and procedures. Critics of conservatism sometimes fail to acknowledge that evidence exists to support the "reality content" of risk assessment procedures or of the risk numbers themselves. For example, researchers at the Harvard School of Public Health recently concluded that on average, the linear dose-response function is not unduly conservative; for many chemicals, the best-fitting curve was in fact steeper at low doses than at higher ones. Similar challenges to the notion that the current estimates are systematically conservative come from recent studies of the dispersion models used to predict the movement of pollutants in air and water, which have shown that the models often underpredict actual concentrations, especially when the terrain or atmospheric environment is complicated.

The most direct "reality check" on QRA involves comparing the predictions of animal extrapolation to the actual can-

cer toll among humans exposed to known levels of a particular substance. Such a comparison can only be made for about two dozen substances (for example, cigarette smoke, vinyl chloride, and chromium) where both human and animal data on exposures and tumors are reasonably reliable. The basis for generalization is therefore limited, and the human potency estimates may be nonconservative (they generally come from data on small groups of relatively healthy workers). However, one research group recently found that, on average, conservative extrapolation procedures yield estimates of human cancer potency that agree fairly well with the actual potencies observed in epidemio-

Alternative methods may substitute one set of flaws for another. The prospect of replacing conservative assumptions with "best estimates" of actual risk may be no less problematic than the status quo. Although conservative estimates have been widely derided as "policy choices masquerading as scientific facts," central or average estimates themselves embody subtle value judgments regarding the implicit social costs of erring on the high or low sides. In this respect, best estimates are no better than conservative ones, which simply strike this balance more in favor of caution about underestimation, and may reflect a desire to minimize large absolute errors of underestimation. In addition, while it is desirable to reduce the ambiguity about how conservative estimates of different risks are, one can show that errors in ranking uncertain risks are also endemic even when best estimates are consistently used.

Reframing the question

Many of the problems engendered by the use of conservative risk numbers (as well as their "real" counterparts) can be overcome by one deceptively simple step—abandoning the quest for single estimates of risk in favor of quantitative descriptions of the uncertainty surrounding these numbers. Such descriptions, which would take into account random and systematic sources of uncertainty in potency, exposure, and uptake, would

reveal all of the possible true values of risk and the likelihood associated with each.

If uncertainty analyses became routine, we could move beyond the narrow debate over whether the estimates were too high or too low and could instead choose the degree of conservatism explicitly and with appreciation of the scientific nuances and societal value judgments specific to each case. For example, researchers from the National Institute of Environmental Health Sciences recently conducted an uncertainty analysis showing that if the EPA wanted to retain an estimate of methylene chloride's potency that was a 95th-percentile conservative estimate, it might well have raised the official estimate by a factor of 1.5 (rather than lowering it by a factor of 9, as was

Quantitative uncertainty analyses can also facilitate dialogue between risk managers and the public concerning how much society is willing to pay to reduce the possibility of particular levels of harm, and can help regulators perceive which uncertainties are dominant and thereby set strategies for research. All of these benefits come at a price, however. Uncertainty analyses are expensive to conduct, sometimes difficult to explain, amenable to subtle manipulation by interested parties, and may be foreboding in that they reveal how little the experts actually know about the likelihood of different levels of harm. Nevertheless, the real challenge of QRA in the next decade will be to recognize that while acknowledging uncertainty may be as difficult as stepping out of one's own shadow, only through the attempt can we discern from what direction the shadows are cast and in which directions to move so that they might ebb.

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Health and Safety Risk Analyses: Information for Better Decisions

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Knowing the nature and magnitude of health and safety risks is helpful in setting priorities as well as in making decisions about pursuing recreational activities, foods, jobs, and other aspects of everyday living. "Risk-risk" situations require a choice among risky alternatives. "How safe" situations involve a more general choice as to how much of other desired activities to sacrifice for increased safety. "How safe" situations are inherently more difficult to manage, because they are subject to fuzzy thinking and rhetoric. The large uncertainties of current estimates must be conveyed explicitly to arrive at sensible decisions.

HAT WOULD YOU DO. IN THE FOLLOWING SITUATIONS:

(i) You have a partially blocked coronary artery that can be treated by bypass surgery or medication. Although there is a chance of dying during surgery, if you survive you can expect less pain and a more active life than from medication. (ii) Your neighborhood school contains asbestos materials. School officials can ignore the problem or pay for the removal of the asbestos with funds from educational programs or a special property tax.

These two situations exemplify the types of health and safety hazards that all of us face (1). Intelligent decisions are needed on which potential hazards to ignore and how much risk reduction to seek. These elecisions require information about the nature and probability of the hazard, how the risk is perceived, and safety goals.

The available data and tools to provide this information are replete with uncertainty, which complicates the decision process and occasionally negates the value of an analysis. The hard choices are clothed in uncertainty and conflicting goals. People feel deeply about health and safety issues but become uncomfortable when thinking about situations that involve danger to their children or to themselves.

The coronary heart disease situation has risks and benefits associated with both choices. With such "risk-risk" situations, a person must select the better alternative (2). For the asbestos situation, the probability of cancer can be lowered, but only by giving up other desired services or activities. In such "how safe is safe enough" situations, society must decide how much should be sacrificed to reduce risk. Each successive reduction in risk generally achieves a bit less and costs a little more, such as when reducing the levels of trace carcinogens in drinking water (3).

Despite the inevitable uncertainties, risk analysis has much to

contribute to risk management. Risk analysis helps identify significant hazards, stimulates basic research, and spotlights the need to agree on health goals and priorities. In the past decade risk quantification has challenged much of the conventional wisdom about the safety of our technologies and the efficacy of particular interventions.

Risk Analysis in Medical Decision-Making

Progress in science enhances understanding of the possible sources of harm and allows quantification of the probabilities, at least crudely. For example, one to two patients out of 100 die during bypass surgery (4). This datum simplifies the "risk-risk" situation for many people who would regard this probability as small in comparison with other dangers in this situation. But some individuals are at extraordinary risk. The tabulated frequency of deaths is the accumulated experience from many surgeons, hospitals, and patients of diverse characteristics. The chance of death during surgery would be much less for a 40-year-old in good physical condition with no other medical problems than for an 80-year-old with severe deterioration of the heart muscle and an inexperienced surgeon.

An individual's perception of the value of outcomes and desire for certainty are important determinants in the decision (5). A sports enthusiast might regard medical treatment of coronary heart disease as useless. Someone afraid of "dying on the table" might elect medical treatment instead of surgery. A patient without insurance would see the large costs associated with surgery. Even the way the outcomes are described, whether in terms of probability of dying or probability of survival, is likely to affect the choice of treatment (6). There is no single optimal decision for all people.

The key issues in medical decision-making are the extent and quality of information about the outcomes of alternative interventions, the incentives influencing the ill person and those treating him, and the preferences of those involved (7). Occasionally, decisions are as simple as treating a broken bone: information is good, treatment is beneficial and carries few complications, and there is a dominant decision. More generally, getting the right information is difficult or impossible. For example, a specialist in one mode of treatment finds it difficult to be neutral in offering advice because of his confidence in his skill and approach, his unfamiliarity with other approaches, and the financial incentive. Even the best available data bristle with snares. For example, cigarette smoking is the most important public health issue. Yet there is no confident answer to individuals who ask about their risk from smoking. Even a more-than-two-pack-a-day smoker has only a 15.6% chance of dying of a smoking-related disease before age 65 (36.4% before age 85); thus, some individuals, for genetic or other reasons, are more susceptible than others (8).

Risk analysis has enlightened decision-making in two ways. First it has allowed quantification of the chances of adverse outcomes

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more precisely as well as of the quality of life and life expectancy implications of alternative modes of treatment. Second, it promotes the evaluation of treatment modes and individual performers. Many treatment modes have been found to be without efficacy, for example, routine removal of tonsils or radical mastectomies (7); some hospitals or surgeons have relatively poor outcomes, such as surgeons doing only a few coronary bypass operations each year (4).

Risk estimates are even more important in evaluating screening and preventive care, since individuals are counselled to seek these services (9). For this counsel to be ethical, not only must the action not be harmful, it must have a reasonable chance of benefiting the person. For example, on average 7.58% of U.S. women contract breast cancer. Early detection (through screening by physical examination plus x-ray) and treatment was found to decrease breast cancer mortality 40% (10). However, the screening is not an unalloyed benefit since a single mammogram in a 35-year-old woman involving a dose of 1 rad would increase the chance of cancer to between 7.59 and 7.61%. For annual examinations, the chance of cancer would rise to between 7.90 and 8.25%. Thus, mammography can have an appreciable risk. Screening at an earlier age or more examinations would increase the chance of radiogenic cancer, while offering diminishing incremental benefit in detecting disease. Although modern equipment has reduced the dose per plate about 50fold, a screening protocol must balance the hazards of screening against those of undetected disease, considering the risk factors for each group.

Some modern equipment is designed to use more than twice as many x-rays per examination as in the clinical trial that showed efficacy. A Pittsburgh physician reports that in more than half the baseline examinations, radiologists recommend retesting because of some suspicious aspect of the film (11). The quest for greater certainty appears to have led some radiologists to increase the chance of inducing cancer, with presumably little improvement in detection. While the increased sensitivity of the equipment has lowered the dose per plate significantly, there is still a need to be concerned about inducing radiogenic cancer. Some radiologists appear to be making a decision about how much uncertainty to tolerate without calculating the benefits and risks of the extra plates and follow-up test. A risk-benefit calculation is needed and plates should be eliminated where they do not change treatment or are done only to avoid malpractice suits. A similar question occurs, although in less dramatic form, when physicians order additional tests that do not have health threats but do increase costs. How much should society be willing to pay to reduce risk?

Quantification of Risk

The dangers of being in a building with undamaged asbestos materials can be quantified for the "how safe" situation. The probability of children getting mesothelioma or lung cancer from such asbestos exposure in school is estimated to be about five per million lifetimes, less than 1/5000 the chance of death faced by these children from other current events in their lives (12). This analysis leads some to neglect asbestos in order to concentrate on reducing other risks, such as reducing time spent in the same room as cigarette smokers, wearing seat belts, or improving the quality of children's education and personal consumption. Others regard this additional risk from asbestos as nontrivial and want it removed. Careless removal of asbestos, however, can pose major risks to the workmen as well as to the children; many experts believe that asbestos in good repair ought to be left in place and removed only when there is a major renovation or a building is demolished (13).

At the current state of knowledge, quantifying risk is somewhat

arbitrary. The estimated probabilities have large margins of uncertainty and are calculated from populations that may be quite unlike the individual having to make a decision. It is not a comfort to know that, on average, exposure to arsenic, chromium, or coke oven gases is not a major source of cancer in the United States if you live just downwind of a major emissions source (14).

The best probability estimates would come from a "perfect" (controlling for confounding factors) epidemiology study on the population of interest at the range of doses or exposures of interest. There are no such studies, however, and, for most hazards, no human data at all. Epidemiology studies always have one or more of the following problems: too few subjects for confident conclusions, failure to control for important confounding factors, no data (or little data) on exposure, exposure levels many times greater than the standards being considered, inadequate diagnosis, subjects lost to follow-up, or subjects who are qualitatively different from the population to be protected. The Environmental Protection Agency (EPA) classifies epidemiology studies as sufficient, limited, or inadequate and then disregards the inadequate studies (15). Since experimental manipulation is not possible, a hard-nosed critic would regard every study as inadequate. Rather, scientists have to ask what can be learned from each study and the studies taken together, and how much confidence can be placed in the results (16).

Often, probabilities must be estimated from laboratory studies. Extrapolation of data from rodents or cultured cells to people is fraught with difficulties (17, 18). Since humans do not have zymbal glands, how should one interpret a study finding that a chemical causes cancer in the zymbal gland of rats? Until science is able to clarify the implications of such findings, regulators usually make the most conservative (that is, worst case), plausible assumption in each situation—for example, any chemical that increases the number of tumors (benign or malignant) in rodents (even in the zymbal gland) is assumed to be carcinogenic in people. The hope is that improvement in scientific understanding will obviate the need for arbitrary assumptions. Initial data on pharmacokinetics and DNA adducts are beginning to clarify critical issues (19). To date regulatory agencies seem reluctant to use these data when they imply lower estimated risks. But regulators must remember that current practice is based on assumptions rather than data; insisting that the current, somewhat arbitrary, assumptions cannot be changed until there is scientific consensus on a new approach is to choose assumptions based on little or no data over models validated by data.

In estimating probabilities from either human or rodent data, the standard assumption is that incidence is proportional to dose measured in milligrams per kilogram of body weight or body surface area (a linear, no threshold dose-response relation), a conservative assumption but still one that is plausible in some cases. Data from both epidemiology and rodent studies show that linearity is the best assumption over a wide range for carcinogens such as ionizing radiation (20). For some carcinogens, halving the dose reduces the number of tumors by less than half, whereas for most chemicals tested, halving a large dose more than halves the number of tumors. The extreme case occurs for carcinogens that are essential nutrients. Levels of chromium and nickel essential for nutrition are estimated to cause a small number of cancers (21).

Finally, current practice for EPA in carcinogen assessment is not to use the best (maximum likelihood or central tendency) estimate of the linear term coefficient in a multistage model. Rather, they construct a 95% confidence interval about that estimated coefficient and use the upper bound (22).

Although conservative assumptions are the rule, there are several places where the risk estimates might understate the true risk. First, people are not exposed to a single chemical, but rather to a number of chemicals. Even if they act independently, the risk will be the sum

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of individual chemical risks. Second, the chemicals may interact and potentiate or dampen the effects of other chemicals. Third, some individuals may be particularly sensitive to some chemicals, more so than the roclents used in testing.

Nonetheless, agency risk assessors believe that, in general, their risk estimates overstate the true risks. In many cases there may be no risk to humans associated with current exposure levels. While ther is still some chance that the risk estimates may understate true risks, agencies find that there is little threat associated with many environmental situations that cause popular concern, such as asbestos in good repair in buildings (12, 14, 23, 24). In contrast, the estimated risk associated with some hazards, such as radon in buildings, is extremely high for some homes (as high as 10,000 per millior lifetimes), arsenic emissions from smelters (as high as 360,000 per million lifetimes), and some food contaminants (the tolerance level for aflatoxin in corn implies 700 cancers per million lifetimes) (14). Current levels of public concern are not closely aligned to the estimated risk level (25).

The value and even the interpretation of risk estimates are compromised by arbitrary assumptions, some conservative and some that would understate the true risk. Arbitrary assumptions inject scientists' personal goals or interpretations of public desires into the risk analysis. Rather, the risk analysis should reflect the best science, the range of plausible models, and judgments, based on the best science, of the appropriate confidence intervals about these estimates. The risk managers need unbiased information with the uncertainties displayed explicitly to help them arrive at good decisions. Regulatory agencies should arrive at similar risk estimates for a substance. The risk management decisions may differ across agencies, depending on the goals embodied in the statutes and the individual costs and benefits of control.

Food Additives

Food additives can introduce hazards and tend to elicit a great deal of emotional response (26). "Risk-risk" situations occur, as when sodium nitrite increases the chance of cancer but reduces the chance of botulism. More frequent are "how safe" situations, where food additives improve the flavor, appearance, or shelf life of food but also increase the chance of cancer. Is having brightly colored maraschino cherries worth even a minuscule threat (the risk of red food color is estimated to be 0.02 cancer per million lifetimes) (14):

Consumers do not "need" nonnutritive sweeteners, color additives, or antioxidizers; food can be less sweet, can be sweetened with sugar, need not have vibrant colors, and can be susceptible to spoiling more quickly. To some people, these properties are of little value; when foods are properly labeled, they select food without additives. To others, these properties are important and worth a tiny increase in the chance of cancer. As long as people understand the hazards, they can make their own choices. For saccharin-sweetened foods, Congress has required that the label must indicate ingredients and that warning signs be posted informing people of the carcinogenic potential.

The mandate of the Food and Drug Administration (FDA) is to prevent food from becoming contaminated or adulterated; the FDA is to ensure that the food supply is healthy (and varied and not needlessly expensive) (26). That mandate requires that the FDA define standards for what is aesthetically acceptable and what is safe enough. The FDA has evolved a policy that if a food additive (or its metabolites or breakdown products) increases the chance by less than one cancers per million lifetimes, the threat is considered to be too small to be of concern (27). This policy is highly controversial

and the subject of litigation. However, given the natural toxic substances in food, it is unclear what a sensible alternative would be (28). The FDA finds the upper bound cancer probabilities for some food constituents and contaminants to be much larger than the comparable figure for food additives (one cancer per million lifetimes or less). For example, the tolerance level of aflatoxin in cor is estimated to increase the incidence of cancer by as much as 70, per million lifetimes (14).

What is the meaning of an estimated probability such as one cancer per million lifetimes (29)? The actual chance might well be zero, since a rodent carcinogen might not be a human carcinogen, or it might be larger, because humans are more sensitive to this chemical than rodents. Applied to the United States, this estimate literally means 230 cancers over 70 years or 3 to 4 additional cancers each year, added to the 1 million "background" cancers. In particular, food colors, such as those used in coloring fruit cocktail, increase the risk about 0.4 cancer per million lifetimes, or about one cancer each year for the U.S. population.

As long as people are presumed to be reasonably well informed and to be capable of making their own judgments, those who like vibrant colored fruit cocktail can consume it while others can avoid it. However, if this food is consumed by someone ignorant of the risks, such as a child, society must decide whether the food colors should be banned. Apparently, the FDA considers a risk estimate of one cancer per million lifetimes to be small enough to let individuals make their own decisions, even if there are some people who take the risk without realizing it.

Traumatic Injuries and Death

Risk assessment has had a long history in analysis of "accidents." In 1985, 92,500 Americans were killed (about 5% of all deaths) and 9 million persons sustained disabling injuries from accidents (30 Almost half the deaths (45,600) were highway-related, 11,600 were work-related, 20,500 occurred at home, and 19,000 were other public accidents. Almost 60 million people were injured, resulting in 543 million restricted activity days. Safety analysts dislike the term "accident" since it has a connotation of being beyond human control. Instead, each trauma injury has a cause, and steps could have been taken to avoid it or at least mitigate the injury.

"Risk-risk" situations occur in designing safety equipment. If an energy-absorbing steering column in an automobile is designed to protect the driver during a low-speed crash, it offers less protection in a high-speed crash, and vice versa. One "how safe" situation is the controversy over whether air bags should be mandated in cars. There is no doubt that air bags would save lives, but the cost per life saved would be about \$1 million (31).

A variety of approaches have been used to assess the frequencies and mitigation possibilities (32). The most important is statistical analysis to identify the frequency of events and conditions leading to injury or death. Others include crash investigation, injury epidemiology, behavioral feedback, economic approaches, human factors, and more recently, the use of fault and event trees (32). The last approach is embodied in probabilistic risk analysis, developed for nuclear reactors and now used in other areas (33).

Aside from an occasional enthusiastic speech, no one talks about eliminating trauma—that would require banning activity. Activities such as mountain climbing are chosen by adults who can be presumed to be reasonably informed of the risks. For all activities, society tries to decrease risk by encouraging safe behavior and safer products; enhancing safety stops when the cost and inconvenien of increased safety exceeds the benefit of the safety gains (a "howsafe" decision). The social decision is complicated by human

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reactions to the safer product that could increase risk (34); when people do not use safety features, their use can be mandated (35).

Injury rates have declined markedly over many decades, whether measured by the fatalities per passenger mile for automobiles and commercial aircraft or occupational injury rates (30). Most of this decline is not related to governmental standards and inspection, but rather seems to come from company and consumer decisions as influenced by legal liability (36).

Risk Management

Risk analysis is done to enlighten decisions about "how safe" and "risk-risk" situations (37). Since the risk estimates have major uncertainties, they may be useless to the risk manager. If a toxic chemical is inexpensive to control or replace, even a hint of toxicity might lead to control (38), such as occurred in the banning of cyclamate. If a chemical is difficult to replace, such as vinyl chloride monomer or saccharin in 1978, it is unlikely to be banned even if the number of deaths associated with its use is nontrivial (39).

Although the dose-response relation has received the most attention, for health risks, exposure assessment adds greater uncertainty. This is anomalous since improving exposure assessment is not difficult.

Providing warning labels and signs does not guarantee that people will read them or understand them (40). However, there is a basic social choice about the extent to which individuals should be allowed to make their own decisions and to be able to understand the information provided and the consequences of their choices. None of this means that the victim and others will not be terribly sorry when a chance is taken and it turns out badly. What range of hazardous choices will society allow to individuals (41)? What information should be available to inform these decisions? Society is not and cannot be expected to maintain consistency, since these are hard decisions. For example, society allows individuals to smoke cigarettes while forbidding them to eat swordfish containing levels of mercury that pose a far lower risk. In some states a person traveling by car to spend a day hang gliding must buckle his seat belt.

Some hazards, such as those associated with a nuclear reactor or a plant making pesticides, endanger people in the vicinity; the decision concerning where to locate them is inherently social in nature since the individuals living nearby will have to accept this risk. Some of these people will see the plant as offering a trivial increase in risk, but others will see it as life threatening. Because individuals can do little to adjust their risk level, these situations exasperate those who disagree with the social decision (42).

"Risk-risk" situations require a balancing. This structure precludes rhetoric about being willing to spend anything to prevent a premature death. The "how safe" situation invites fuzzy thinking and rhetoric. The issue is not how many pieces of green paper are worth preventing a premature death, but rather how much inconvenience and discomfort to bear and how much consumption of other goods and services to give up to lower the probability of disease or death a bit more (43).

A person may appear to engage in inconsistent behavior in smoking cigarettes while worrying about food additives or not testing for radon while worrying about asbestos that is in good repair. The apparent contradictions may result from a complicated cognitive structure for perceiving hazardous situations (25). People are concerned with aspects different from those that experts focus on. Since they are the consumers and the voters in our democracy, people are the final arbiters of how safe is safe enough.

For guidance on what risk levels to set, a variety of approaches has been used. One attempts to find what is a trivial or de minimis risk,

so that the limited resources for improvement are not wasted to reduce risks beyond this level (14, 44). A second approach is to examine hazards that are readily accepted in everyday life and in regulations (29). A third is to seek public guidance through referendums or through the actions of elected representatives. Several state referendums on nuclear power have done little to clarify public preferences; each was voted down but each was phrased in such an extreme form that a moderate critic of nuclear power might have voted against the measure. Congress has not been much more informative, since legislation generally contains contradictory language. For example, the Occupational Safety and Health Act sets a goal" "... that no employee will suffer material impairment of health or functional capacity . . . "; however, the act also requires that the regulations "... assure insofar as practicable..." which is interpreted to mean both technical and economic feasibility. In one of the few cases where Congress was unequivocal about setting a stringent risk standard, the Delaney amendment to prohibit carcinogenic food additives, the FDA has permitted them, as long as they pose a tiny risk (17, 27). Congress, the agencies, and the courts are concerned that safety regulations not be so stringent as to halt the economy or even shut an industry. The result is that Occupational Safety and Health Act and EPA sometimes tolerate extremely large hazards because it is not technically or economically feasible to deal

Just as a great advantage of risk assessment is bringing the calculations out into the open, uncertainties and all, so one of the great advantages of risk management has been bringing the decision process out into the open. Since the probabilities cannot be lowered to zero, there is good reason to inform the affected parties and the public of the basis for a decision. While it is time consuming and apparently wasteful to reach these decisions in a fishbowl, there is no other process likely to secure public confidence and consent.

Conclusion

Risk analysts should not attempt to overstate or understate threats, but rather to give a best estimate and the range of uncertainty. Decision-makers can choose the proper amount of conservatism in setting the standard. The various federal agencies ought to coordinate their risk assessment processes so that they will arrive at similar estimates for a particular hazard.

Current risk estimates are fraught with uncertainty. The process of conducting and defending risk analyses highlights these uncertainties and suggests a research agenda to resolve them. Rather than reify existing arbitrary assumptions, the process must be opened to new data and models, particularly since current assumptions often are based on little or no data.

It is inherently easier to manage "risk-risk" situations than "how safe" situations. The former are self-limiting and require an explicit balancing of the risks. The latter are subject to rhetoric about zero risk because there is no necessity to consider what is being sacrificed to lower the probability further. Risk management is inherently difficult not only because it requires setting specific goals, but because the situations involved often affect many people simultaneously, requiring a collective decision. Since people have different safety goals and are uncomfortable thinking about hazardous situations, collective decisions are difficult.

Progress in the field of risk analysis has been enormous—it hardly existed a decade ago. The intellectual ferment comes from the focus on helping to enlighten decisions, rather than on intellectual elegance. The constant interaction of those involved in risk analysis and in risk management is needed to stimulate analysts to make their greatest contribution.

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- C. Start, Science 165, 1232 (1969); W. W. Lowrance, Of Acceptable Risk (Kaufmann, Los Altos, CA, 1976); W. D. Rowe, An Anatomy of Risk (Wiley, New York, 1977)
- 2. L. B. Lave, The Strategy of Social Regulation (Brookings Institution, Washington, DC, 1981)
- National Research Council, Drinking Water and Health (National Academy Press, Washington, DC, 1986), vol. 6.
 M. C. Wrinstein and W. B. Stasson, Annu. Rev. Public Health 6, 41 (1985).
 B. J. McNeil and S. G. Pauker, ibid. 5, 135 (1984).

- B. J. McNeil and S. G. Pauker, ibid. 5, 135 (1984).
 H. C. Sox, Jr., A. Tversky, N. Engl. J. Med. 306, 1259 (1982).
 J. P. Burker, B. Barnes, F. Mosteller, Eds., Catts, Risk, and Benefits of Surgery (Oxford Univ. Press, New York, 1977); Institute of Medicine, Assessing Medical Technologies (National Academy Press, Washington, DC, 1985).
 R. Doll and R. Peto, Br. Med. J. 2, 1525 (1976); L. E. Kuller, E. Meilahn, M. Townsend, G. Weinberg, Annu. Rev. Public Health 3, 153 (1982).
 J. R. Lave et al., in Preventive Medicine, USA (Prodist, New York, 1976), p. 675; J. R. Lave and L. B. Lave, Health Soc. 55, 273 (1977); L. B. Russell, Is Prevention Better than Cure? (Brookings Institution, Washington, DC, 1986).
 U.S. Department of Health and Human Services, Determining Risks to Health: Federal Policy and Practice (Auburn, Dover, MA, 1986), pp. 219–223; L. H. Baker, CA Caruer J. Clin. 32, 194 (1982); J. K. Gohagen, W. P. Darby, E. L. Spitznagel, B. S. Monsees, A. E. Tome, J. Natl. Cancer Inst. 77, 71 (1986).
 B. Block, personal communication.
- 11. B. Block, personal communication.
- 12. R. Doll and J. Peto, Ashestos: Effects on Health of Exposure to Ashestos (Her Majesty's Stationery Office, London, 1985); H. Weill and J. M. Hughes, Annu. Rev. Public
- Stationery Office, London, 1985); H. Weill and J. M. Hughes, Annu. Rev. Public Health 7, 171 (1986).
 D. C. Dewees, Asharos in Buildings: An Economic Investigation (Resources for the Future, Washington, DC, 1986).
 P. Milvy, Risk Anal. 6, 69 (1986); C. C. Travis, S. A. Richter, E. A. C. Crouch, R. Wilson, Environ. Sci. Technol., in press; D. Byrd and L. B. Lave, De Minimis Risk, C. Whipple, Ed. (Plenum, New York, 1987).
 Environmental Protection Agency, Fed. Regist. 51, 33992 (24 September 1986).
 T. A. Louis, H. V. Fineberg, F. Mosteller, Annu. Rev. Public Health 5, 433 (1984).
 U.S. Office of Technology Assessment. Assessment of Technologies of Determining
- T. A. Louis, H. V. Fincherg, F. Mosteller, Annu. Rev. Public Health 5, 433 (1984).
 U.S. Office of Technology Assessment, Assessment of Technologies of Determining Cancer Rivis from the Environment (U.S. Government Printing Office, Washington, DC, 1981); L. B. Lave, Quantitative Risk Analysis in Regulation (Brookings Institution, Washington, DC, 1982); U.S. Office of Science and Technology Policy, Fed. Regist. 50, 10371 (1985).
 L. B. Lave and G. S. Omenn, Nature (London) 324, 29 (1986).
 D. G. Hoel, R. A. Merrill, F. P. Perera, Eds., Risk Quantification and Regulatory Policy (Baribury Report 19, Cold Spring Harbor Laboratory, Cold Spring Harbor, NY, 1985); I. B. Weinstein, Annu. Rev. Public Health 4, 409 (1983); D. B. Hartis, Risk Anal. 6, 181 (1986); F. Perera, ibid., p. 195.
 National Research Council, The Effects on Populations of Exposure to Low Levels of Ionizing Radiation (National Academy Press, Washington, DC, 1980).
 Cosmetic, Toiletry and Fragrance Association, "Comments on the decision to adopt a de minimis policy under the Delaney Clause" (Washington, DC, 1986).
 E. L. Anderson et al., Risk Anal. 3, 277 (1983).
 J. W. Grisham, Health Aspeats of the Disposal of Waste Chemicals (Pergamon, New York, 1986); M. Russell, Science 236, 286 (1987).

- E. Whelan, Toxic Terror (Jameson, Ottawa, IL, 1985).
 D. Kahneman, P. Slovic, A. Tversky, Judgment Under Uncertainty: Heuristics and D. Kalinellian, P. Slovic, A. Ivelsky, Jungment Uniar Under Universities and Biases (Cambridge Univ. Press, New York, 1982); B. Fischhoff, S. Lichenstein, P. Slovic, R. Keeney, S. Derby, Acceptable Risk (Cambridge Univ. Press, New York, 1981); P. Slovic, Science 236, 280 (1987).
 P. B. Hutt, Food-Drug-Cosmetic Law J. 33, 505 (1978); R. A. Merrill, Mich. Law Rev. 77, 171 (1978); S. A. Miller and M. G. Stephenson, Am. J. Clin. Nutr. 42, 720 (1982)
- 27. Food and Drug Administration, Fed. Regist. 50, 51551 (18 December 1985); I Sun, Science 229, 739 (1985).
- B. N. Ames, Science 221, 1256 (1983).
 B. L. Cohen and I. S. Lee, Health Phys. 36, 707 (1979); R. Wilson and E. Crouch, Science 236, 267 (1987)
- National Safery Council, Accident Facts (National Safety Council, Chicago, 1986);
 P. Baker, B. O'Neill, R. S. Karpf, The Injury Fact Book (Lexington, Lexington) MA, 1984); J. A. Wallet, Injury Control: A Guide to the Causes and Prevention of Trauma (Lexington, Lexington, MA, 1985).

 31. L. B. Lave, Science 212, 893 (1981).

- J. D. Graham and H. Piehler, unpublished observations.
 W. E. Vesely, Risk Anal. 4, 247 (1984).
 L. Evans and R. C. Schwing, Human Behavior and Traffic Safety (Plenum, New York, 1985); W. K. Viscusi, J. Law Econ. 38, 527 (1985).
 E. A. Latimer and L. B. Lave, Am. J. Public Health 77, 183 (1987).
- M. Baram, Alternatives to Regulation (Lexington, Lexington, MA, 1982)
- National Research Council, Risk Assessment in the Federal Government: Managing the Process (National Academy Press, Washington, DC, 1983); W. Ruckleshaus, Issues Sci. Technol. 1, 19 (1985); V. T. Covello and J. Mumpower, Risk Anal. 5, 103 (1985).
- National Research Council, Taxicity Testing: Strategies to Determine Needs and Priorities (National Academy Press, Washington, DC, 1984); L. B. Lave and A. C. Upton, Taxic Substances, Health, and the Environment (Johns Hopkins Univ. Press, Baitimore, 1987).
- J. L. Badaracco, Jr., Loading the Due: A Five-Country Study of Vinyl Chloride Regulation (Harvard Business School Press, Boston, MA, 1985); National Academy of Sciences, Food Safety Policy: Scientific and Societal Considerations (National Academy Press, Washington, DC, 1979).

 A. Morris, M. B. Mazis, I. Barofsky, Product Labeling and Health Risks (Banbury)
- A. Mottis, M. B. Mazis, I. Barotsky, Froduct Labeling and Health Risk (Banbluw)
 Report 6, Cold Spring Harbor Laboratory, Cold Spring Harbor, NY, 1980); W.
 K. Viscusi, W. A. Magaz, J. Huber, Rand J. Eam. 17, 351 (1986); W. K. Viscusi
 and W. A. Magaz, Learning About Risk: Consumer and Worker Responses to Hazard
 Information (Harvard Univ. Press, Cambridge, MA, in press); S. G. Hadden, Read
 the Label: Reducing Risk by Providing Information (Westview, Boulder, CO, 1986).
 D. MacLean, in Risk Evaluation and Management, V. T. Covello, J. Menkes, J.
 Mumpower, Eds. (Plenum, New York, 1986); R. L. Keeney, Risk Anal. 4, 117
 (1984); I. B. Lay Acident Anal Pres. 19, 29 (1987).
- (1984); L. B. Lave, Accident Anal. Prev. 19, 29 (1987). L. B. Lave and T. Romer, Risk Anal. 3, 217 (1983). J. Linnerooth, Inquiry 17, 52 (1979); W. K. Viscusi, Risk by Choice: Regulating Health and Safety in the Workplace (Harvard Univ. Press, Cambridge, MA, 1983).
- Supreme Court, Industrial Union Department, AFL-CIO v. American Petrolev Institute, 448, US 607, 639 (1980).
- 45. I thank D. Byrd, P. Hutt, J. Lave, T. Lave, W. North, P. Slovic, and C. Whipple 1.

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TELLING REPORTERS ABOUT RISK

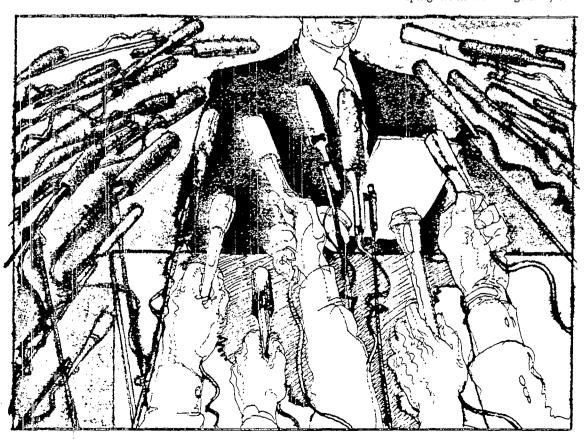
Dealing with reporters needn't be the least agreeable part of the job.

PETER M. SANDMAN

Ithough I hate to admit it, risk communication is a simpler field than risk assessment or risk management. It just isn't that hard to understand how journalists and nontechnical people think about risk. But it is crucial to understand. In fact not mastering the rudiments of risk communication has led a lot of smart people to make a lot of foolish choices.

Much depends on whether you think risk communication is a job that can safely be left to technicians—public relations staff, community affairs officers—or whether you believe it must become an integral part of risk management. My main goal is for environmental protection commissioners and plant managers to read what I have to say, not merely pass it along to the public relations office.

That temptation is almost overwhelming, I know. Dealing with the media seems in so many ways the least pleasant, least controllable, least fair part of a decisionmaker's work. Most risk managers, I suspect, spend a good deal of time hoping the media will go away and



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leave them to do their jobs in peace.

But since they won't, the next best thing is to understand better why they won't, how they are likely to react to what you have to say, and what you might want to say differently next time.

 Environmental risk is not a big story

The mass media are not especially interested in environmental risk. Reporters do care whether or not an environmental situation is risky; that's what makes it newsworthy. But once the possibility of hazard is established, the focus turns to other matters; how did the problem happen, who is responsible for cleaning it up, how much will it cost? Assessing the extent of the risk strikes most journalists as an academic exercise. The reporter's job is news, not education. And the news is the risky thing that has happened, not the difficult determination of how risky it actually is.

The typical news story on environmental risk touches on risk itself, while it dwells on more newsworthy matters. In 1985, newspaper editors in New Jersey were asked to submit examples of their best reporting on environmental risk, and the articles were analyzed paragraph by paragraph. Only 32% of the paragraphs dealt at all with risk. Nearly half of the risk paragraphs, moreover, focused on whether a substance assumed to be risky was or was not present, leaving only 17% of the paragraphs to deal clirectly with riskiness itself. In a parallel study, reporters were asked to specify which information they would need most urgently in covering an environmental risk emergency. Most reporters chose the basic risk information, saving the details for a possible second day story. What happened, how it happened, who's to blame and what the authorities are doing about it all command more journalistic attention than toxicity during an environmental crisis.

• Politics is more newsworthy than science

The media's reluctance to focus on risk for more than a paragraph or two might be less of problem if that paragraph or two were a careful summary of the scientific evidence. It seldom is. In fact, the media are especially disinclined to

cover the science of risk. Most of the paragraphs devoted to risk in the New Jersey study consisted of unsupported opinion-someone asserting or denying the risk without documentation. Only 4.2% of the paragraphs (24% of the risk paragraphs) took an intermediate or mixed or tentative position on the extent of risk. And only a handful of the articles told the readers what standard (if any) existed for the hazard in question, much less the status of research and technical debate surrounding the standard.

Trying to interest journalists in the abstract issues of environmental risk assessment is tough; abstract issues are not the meat of journalism. Yet the public needs to understand abstractions like the uncertainty of risk assessments, the impossibility of zero risk, the debatable assumptions underlying dose-response curves and animal tests. Where possible, it helps to embed some of these concepts in your comments on hot breaking stories.

• Reporters cover viewpoints, not "truths"

For science, objectivity is tentativeness and adherence to evidence in the search for truth. For journalism, objectivity is balance. In the epistemology of journalism, there is no truth (or at least no way to determine truth); there are only conflicting claims, to be covered as fairly as posssible, thus tossing the hot potato of truth into the lap of the audience.

Imagine a scale from 0 to 10 of all possible positions on an issue. Typically, reporters give short shrift to 0, 1, 9 and 10; these views are too extreme to be credible. Reporters may also pay relatively little attention to 4, 5 and 6; these positions are too wishy-washy to make good copy. Most of the news. then, consists of 2's and 3's and 7's and 8's, in alternating paragraphs if the issue is hot, otherwise in separate stories as each side creates and dominates its own news events. Objectivity to the journalist thus means giving both sides their chance, and reporting accurately what they had to say. It does not mean filling in the uninteresting middle, and it certainly does not mean figuring out who is right.

If a risk story is developing and you have a perspective that you feel

has not been well covered, don't wait to be called—you won't be. Reporters are busy chasing after the sources they have to talk to, and listening to the sources who want to talk to them.

Rather than suffer in silence, become one of the relatively few experts who keep newsroom telephone numbers in their rolodexes. You will find reporters amazingly willing to listen, to put your number in their rolodexes, to cover your point of view along with all the others. Insofar as you can, try to be a 3 or a 7—that is, a credible exponent of an identifiable viewpoint. Don't let yourself be pushed to a position that's not yours, of course, but recognize that journalism doesn't trust 0's and 10's and has little use for 5's.

Although journalists tend not to believe in Truth-with-a-capital-T, they believe fervently in facts. Never lie to a reporter. Never guess. If you don't know, say you don't know. If you know but can't tell, say you can't tell and explain why.

• The risk story is usually simplified to a dichotomy

The media see environmental risk as a dichotomy; either the situation is hazardous or it is safe. This is in part because journalism dichotomizes all issues into sides to be balanced. But there are other reasons for dichotomizing risk. (1) It is difficult to find space for complex, nuanced, intermediate positions in a typical news story, say 40 seconds on televesion or 15 short paragraphs in a newspaper. (2) Virtually everyone outside his or her own field prefers simplicity to complexity, precision to approximation, and certainty to tentativeness. (3) Most of the "bottom lines" of journalism are dichotomies-the chemical release is either legal or illegal, people either evacuate or stay, the incinerator is either built or not built. Like risk managers, the general public is usually asked to make yes-or-no decisions, and journalists are not wrong to want to offer information in that form.

If you want to fight the journalistic tendency to dichotomize, fight it explicitly, asserting that the issue is not "risky or not" but "how risky." Recognizing that intermediate positions on risk are intrinsically less dramatic and more com-

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plex than extreme positions, work especially hard to come up with simple, clear, interesting ways to express the middle view. Even so, expect reporters to insist on knowing "which side" you come down on with respect to the underlying policy dichotomy.

• Reporters try to personalize the risk

Perhaps nothing about media coverage of environmental risk so irritates rechnical sources as the media's tendency to personalize. "Have you stopped drinking it vourself?" "Would you let your family live there?" Such questions fly in the face of the source's technical training to keep oneself out of one's research, and they confuse the evidentiary requirements of policy decisions with the looser ones of personal choices. But for reporters, questions that personalize are the best questions. They do what their editors are constantly asking reporters to do: bring dead issues to life, make the abstract concrete, and focus on real people facing real decisions.

Knowing that reporters will inevitably ask personalizing questions, he prepared with answers. It is often possible to answer with both one's personal views and one's policy recommendations, and then to explain the difference if there is one. Or come with colleagues whose personal views are different, thus dramatizing the uncertainty of the data. If you are not willing (or not permitted) to acknowledge your own views, plan out some other way to personalize the risk, such as anecdotes, metaphors, or specific advice for readers and viewers on the individual micro-risk level.

• Claims of risk are usually more newsworthy than claims of safety

On our 0-10 scale of risk assertions, the 3's and 7's share the bulk of the coverage, but they don't share it equally. Risk assertions receive considerably more media attention than risk denials. Sometimes, in fact, the denials get even less coverage than the intermediate position, and reporters wind up "balancing" strong assertions of risk with bland statements that the degree of risk is unknown. In the New Jersey study, the proportions were 58% risky, 18% not risky, and 24% mixed or intermediate.

This is not bias, at least not as

journalism understands bias. It is built into the concept of newsworthiness. If there were no allegation of risk, there would be no story. That something here might be risky is thus the core of the story; having covered it, the media give rather less attention to the counterbalancing notion that it might not be risky.

Among several factors that make risk more newsworthy than safety, the one closest to outright bias—but still distinguishable in the minds of journalists—is the media's traditional skepticism toward those in authority. Most news is about powerful people, but along with the advantage of access government and industry must endure the disadvantage of suspicion. Environmental groups, by contrast, receive less attention from the media, but the attention is more consistently friendly.

Sociologist Allan Mazur has found that public fearfulness about risky new technologies is proportional to the amount of coverage, not to its character. Media coverage of environmental risk alerts the public to risks it was otherwise unaware of, and thus increases the level of alarm even when coverage is balanced.

This is not a rationale for avoiding the media. Even balanced media coverage may not reliably lead to balanced public opinion, but balanced coverage is preferable to unbalanced coverage. And the coverage is most likely to be balanced when sources on all sides are actively trying to get covered. People with knowledge and opinions to share perform a public service when they share them.

• Reporters do their jobs with limited expertise and time

At all but the largest media, reporters covering environmental risk are not likely to have any special preparation for the assignment. Specialized environmental reporters are the exception to the rule. Reporters covering an environmental emergency, for example, are mostly general assignment or police reporters. And reporters tend to be science-phobic in the first place: the typical college journalism major takes only two science courses, and chooses those two carefully to avoid rigor. Though there are many exceptions, the average reporter approaches a technical story with trepidation (often hidden by professional bravado), expecting not to understand.

It doesn't help that the average reporter covers and writes two or three stories a day. Here too there are exceptions, but most journalists are in a great hurry most of the time. They must make deadline not just on this story, but quite often on the story they will be covering after this one. Their goal, reasonably, is not to find out all that is known, but just to find out enough to write the story.

COMMUNICATE

It may help to train reporters about your field—but it will help a lot more to train yourself (and your colleagues and staff) about dealing with the media. Hiring effective public information specialists is also worthwhile, but reporters much prefer to talk to the people in charge. Especially during emergencies, press calls often go the boss and the expert instead of the press office, so the boss and the expert should know how to talk to reporters.

Adequate communication skills are not so hard to develop. All it takes is a little understanding of how the media work, a little training in dealing with reporters, and a little experience to smooth out the rough edges.

Though you may never enjoy your contact with reporters, the risks of ducking the media are far greater than the risks of working with them. Every news story about environmental risk is a collaboration between the journalists working on the story and the sources they talk to. There's not much you can do to change the nature of journalism or the performance of journalists. But you can understand them and figure out how to deal with them. By improving your own performance as a source, you can bring about a real improvement in media coverage of environmental risk.

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